

FILE 'REGISTRY' ENTERED AT 18:10:14 ON 12 DEC 2009  
EXP 2-PHENYLAMINO-9-(4-HYDROXYBUTYL/CN

FILE 'STNGUIDE' ENTERED AT 18:10:37 ON 12 DEC 2009

FILE 'REGISTRY' ENTERED AT 18:12:42 ON 12 DEC 2009  
STRUCTURE uploaded

L1 0 S L1  
L2 2 S L1 SSS FULL

FILE 'HCAPLUS' ENTERED AT 18:13:35 ON 12 DEC 2009  
L4 12 S L3

FILE 'REGISTRY' ENTERED AT 09:58:12 ON 14 DEC 2009  
EXP ACYCLOVIR MONOPHOSPHATE/CN

L1 1 S E3  
EXP GANCYCLOVIR MONOPHOSPHATE/CN  
EXP GANCICLOVIR MONOPHOSPHATE/CN  
EXP GANCICLOVIR- MONOPHOSPHATE/CN  
EXP GANCICLOVIR-O-MONOPHOSPHATE/CN  
EXP GANCICLOVIR/CN  
EXP CIDOFOOVIR/CN  
L2 1 S E4  
EXP FOSCARNET/CN  
L3 1 S E3

FILE 'HCAPLUS' ENTERED AT 10:00:25 ON 14 DEC 2009

L4 1216 S L1/THU OR L2/THU OR L3/THU  
L5 30155 S HERPES  
L6 218 S L4 AND L5  
L7 128 S L6 AND (PY<2003 OR AY<2003 OR PRY<2003)  
L8 10740 S THYMIDINE KINASE  
L9 21 S L7 AND L8  
L10 27 S (GANCYCLOVIR OR GANCICLOVIR) (2A) (PHOSPHATE OR MONOPHOSPHATE)  
L11 51214 S HERPES OR HERPESVIRUS  
L12 10 S L10 AND L11  
L13 9 S L12 AND (PY<2003 OR AY<2003 OR PRY<2003)

=> file registry			
COST IN U.S. DOLLARS	SINCE FILE	TOTAL	
FULL ESTIMATED COST	ENTRY	SESSION	
	0.22	0.22	

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STRUCTURE FILE UPDATES: 11 DEC 2009 HIGHEST RN 1197154-31-6  
 DICTIONARY FILE UPDATES: 11 DEC 2009 HIGHEST RN 1197154-31-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 26, 2009.

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/support/stngen/stndoc/properties.html>

=> exp 2-phenylamino-9-(4-hydroxybutyl)/cn			
E1 1 2-PHENYLAMINO-8-PROPYL-8H-PYRIDO(2,3-D)PYRIMIDIN-7-ONE/CN	SINCE FILE	TOTAL	
E2 1 2-PHENYLAMINO-8H-PYRIDO(2,3-D)PYRIMIDIN-7-ONE/CN	ENTRY	SESSION	
E3 0 --> 2-PHENYLAMINO-9-(4-HYDROXYBUTYL/CN			
E4 1 2-PHENYLAMINO-N-(2-(PIPERIDIN-1-YL)ETHYL)-6-(4-(3-((PYRIDIN-3-YL)METHYL)UREIDO)PHENYL)NICOTINAMIDE/CN			
E5 1 2-PHENYLAMINO-N6,2'-O-DIMETHYLADENOSINE/CN			
E6 1 2-PHENYLAMINO-N6,3'-O-DIMETHYLADENOSINE/CN			
E7 1 2-PHENYLAMINOADENOSINE/CN			
E8 1 2-PHENYLAMINOBENZAMIDE/CN			
E9 1 2-PHENYLAMINOBENZOPHENONE/CN			
E10 1 2-PHENYLAMINOETHYL METHACRYLATE/CN			
E11 1 2-PHENYLAMINOINDAN/CN			
E12 1 2-PHENYLAMINOMETHYL-2'-BIPHENYLCARBOXYLIC ACID/CN			

=> file stnguide			
COST IN U.S. DOLLARS	SINCE FILE	TOTAL	
FULL ESTIMATED COST	ENTRY	SESSION	
	0.48	0.70	

FILE 'STNGUIDE' ENTERED AT 18:10:37 ON 12 DEC 2009  
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FILE CONTAINS CURRENT INFORMATION.  
 LAST RELOADED: Dec 11, 2009 (20091211/UP).

=> file registry			
COST IN U.S. DOLLARS	SINCE FILE	TOTAL	
FULL ESTIMATED COST	ENTRY	SESSION	
	0.21	0.91	

FILE 'REGISTRY' ENTERED AT 18:12:42 ON 12 DEC 2009  
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STRUCTURE FILE UPDATES: 11 DEC 2009 HIGHEST RN 1197154-31-6  
DICTIONARY FILE UPDATES: 11 DEC 2009 HIGHEST RN 1197154-31-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 26, 2009.

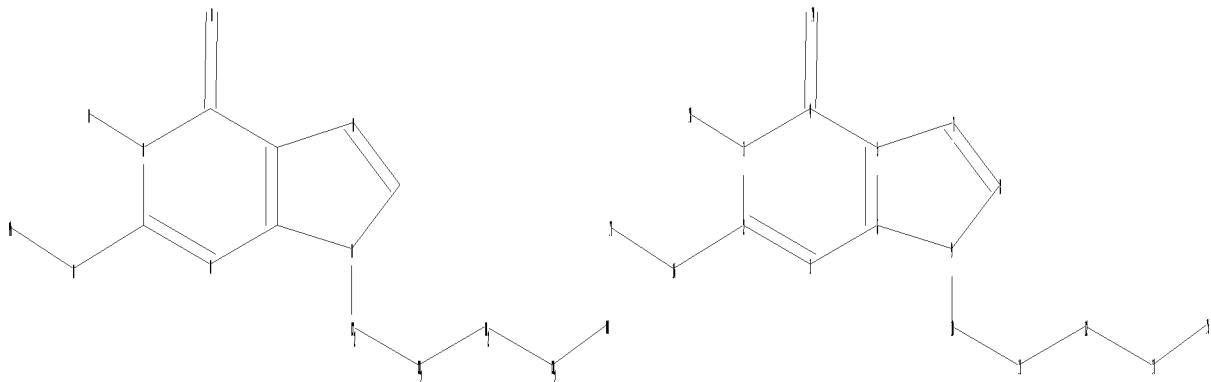
Please note that search-term pricing does apply when  
conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and  
predicted properties as well as tags indicating availability of  
experimental property data in the original document. For information  
on property searching in REGISTRY, refer to:

<http://www.cas.org/support/stngen/stndoc/properties.html>

=>

Uploading C:\Program Files\STNEXP\Queries\10767019oxopurine.str



chain nodes :  
10 11 12 13 14 15 16 17 18  
ring nodes :  
1 2 3 4 5 6 7 8 9  
chain bonds :  
2-16 3-18 4-14 9-10 10-11 11-12 12-13 13-15 16-17  
ring bonds :  
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-9 7-8 8-9  
exact/norm bonds :  
1-2 1-6 2-3 2-16 3-4 4-5 4-14 5-6 5-7 6-9 7-8 8-9  
exact bonds :  
3-18 9-10 10-11 11-12 12-13 13-15 16-17

Match level :  
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:CLASS  
11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS

L1 STRUCTURE UPLOADED

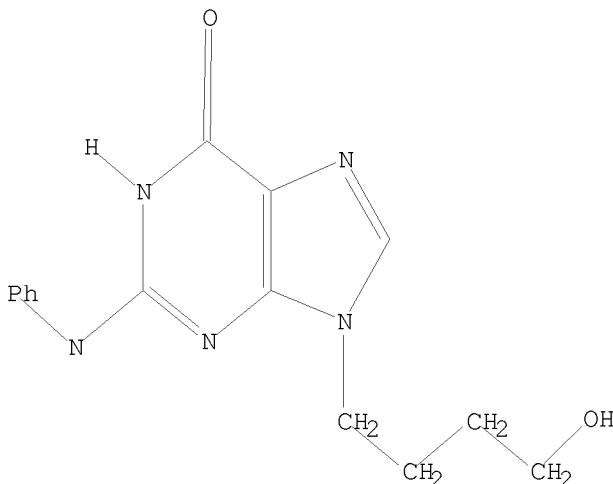
=> s 11  
SAMPLE SEARCH INITIATED 18:12:54 FILE 'REGISTRY'  
SAMPLE SCREEN SEARCH COMPLETED - 0 TO ITERATE

100.0% PROCESSED 0 ITERATIONS 0 ANSWERS  
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*  
BATCH \*\*COMPLETE\*\*  
PROJECTED ITERATIONS: 0 TO 0  
PROJECTED ANSWERS: 0 TO 0

L2 0 SEA SSS SAM L1

=> d 11  
L1 HAS NO ANSWERS  
L1 STR



Structure attributes must be viewed using STN Express query preparation.

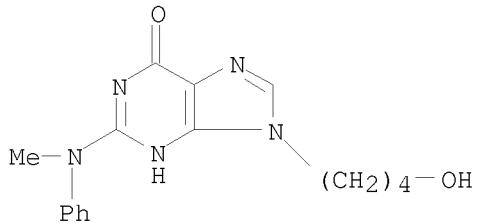
=> s 11 sss full  
FULL SEARCH INITIATED 18:13:16 FILE 'REGISTRY'  
FULL SCREEN SEARCH COMPLETED - 21 TO ITERATE

100.0% PROCESSED 21 ITERATIONS 2 ANSWERS  
SEARCH TIME: 00.00.01

L3 2 SEA SSS FUL L1

=> d 13 scan

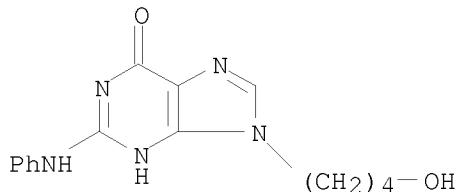
L3 2 ANSWERS REGISTRY COPYRIGHT 2009 ACS on STN  
IN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(methylphenylamino)-  
MF C16 H19 N5 O2



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L3 2 ANSWERS REGISTRY COPYRIGHT 2009 ACS on STN  
 IN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(phenylamino)-  
 MF C15 H17 N5 O2



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

ALL ANSWERS HAVE BEEN SCANNED

=> file hcaplus		SINCE FILE	TOTAL
COST IN U.S. DOLLARS		ENTRY	SESSION
FULL ESTIMATED COST		185.88	186.79

FILE 'HCAPLUS' ENTERED AT 18:13:35 ON 12 DEC 2009  
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FILE COVERS 1907 - 12 Dec 2009 VOL 151 ISS 25

FILE LAST UPDATED: 11 Dec 2009 (20091211/ED)

REVISED CLASS FIELDS (/NCL) LAST RELOADED: Oct 2009

USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2009

HCAplus now includes complete International Patent Classification (IPC) reclassification data for the third quarter of 2009.

CAS Information Use Policies apply and are available at:

<http://www.cas.org/legal/infopolicy.html>

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 13

L4 12 L3

=> d 14 1-12 ti abs bib hitstr

L4 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN

TI Sensitivity of monkey B virus (*Cercopithecine herpesvirus 1*) to antiviral drugs: role of thymidine kinase in antiviral activities of substrate analogs and acyclonucleosides

AB Herpes B virus (B virus [BV]) is a macaque herpesvirus that is occasionally transmitted to humans where it can cause rapidly ascending encephalitis that is often fatal. To understand the low susceptibility of BV to the acyclonucleosides, we have cloned, expressed, and characterized the BV thymidine kinase (TK), an enzyme that is expected to "activate" nucleoside analogs. This enzyme is similar in sequence and properties to the TK of herpes simplex virus (HSV), i.e., it has a broad substrate range and low enantioselectivity and is sensitive to inhibitors of HSV TKs. The BV enzyme phosphorylates some modified nucleosides and acyclonucleosides and L enantiomers of thymidine and related antiherpetic analogs. However, the potent anti-HSV drugs acyclovir (ACV), ganciclovir (GCV), and 5-bromovinyldeoxyuridine were poorly or not phosphorylated by the BV enzyme under the exptl. conditions. The antiviral activities of a number of marketed antiherpes drugs and exptl. compds. were compared against BV strains and, for comparison, HSV type 1 (HSV-1) in Vero cell cultures. For most compds. tested, BV was found to be about as sensitive as HSV-1 was. However, BV was less sensitive to ACV and GCV than HSV-1 was. The abilities of thymidine analogs and acyclonucleosides to inhibit replication of BV in Vero cell culture were not always proportional to their substrate properties for BV TK. Our studies characterize BV TK for the first time and suggest new lead compds., e.g., 5-ethyldeoxyuridine and pencyclovir, which may be superior to ACV or GCV as treatment for this emerging infectious disease.

AN 2007:636814 HCAPLUS <<LOGINID::20091212>>

DN 147:203162

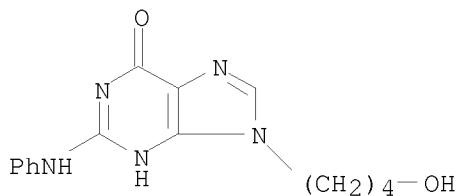
TI Sensitivity of monkey B virus (*Cercopithecine herpesvirus 1*) to antiviral drugs: role of thymidine kinase in antiviral activities of substrate analogs and acyclonucleosides

AU Focher, Federico; Lossani, Andrea; Verri, Annalisa; Spadari, Silvio; Maioli, Andrew; Gambino, Joseph J.; Wright, George E.; Eberle, Richard; Black, Darla H.; Medveczky, Peter; Medveczky, Maria; Shugar, David

CS Istituto di Genetica Molecolare, Consiglio Nazionale delle Ricerche, Pavia, 27100, Italy

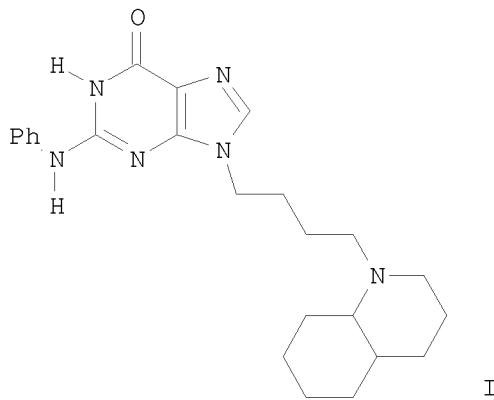
SO Antimicrobial Agents and Chemotherapy (2007), 51(6), 2028-2034

CODEN: AMACQ; ISSN: 0066-4804  
 PB American Society for Microbiology  
 DT Journal  
 LA English  
 IT 161363-19-5  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (monkey B virus thymidine kinase activity related to sensitivity to  
 antiviral acyclonucleosides and thymidine analogs)  
 RN 161363-19-5 HCPLUS  
 CN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(phenylamino)- (CA INDEX  
 NAME)



OSC.G 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)  
 RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

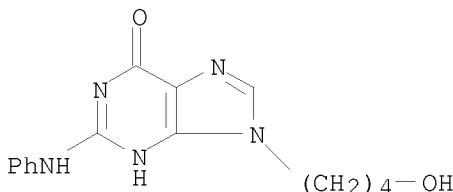
L4 ANSWER 2 OF 12 HCPLUS COPYRIGHT 2009 ACS on STN  
 TI Inhibition of Herpes Simplex Virus Thymidine Kinases by  
 2-Phenylamino-6-oxopurines and Related Compounds: Structure-Activity  
 Relationships and Antiherpetic Activity in Vivo  
 GI



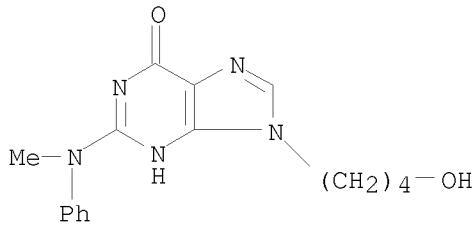
AB Derivs. of the herpes simplex thymidine kinase inhibitor HPG  
 [2-phenylamino-9-(4-hydroxybutyl)-6-oxopurine] have been synthesized and  
 tested for inhibitory activity against recombinant enzymes (TK) from  
 herpes simplex types 1 and 2 (HSV-1, HSV-2). The compds. inhibited  
 phosphorylation of [<sup>3</sup>H]thymidine by both enzymes, but potencies differed  
 quant. from those of HPG and were generally greater for HSV-2 than HSV-1

TKs. Changes in inhibitory potency were generally consistent with the inhibitor/substrate binding site structure based on published X-ray structures of HSV-1 TK. In particular, several 9-(4-aminobutyl) analogs with bulky tertiary amino substituents were among the most potent inhibitors. Variable substrate assays showed that the most potent compound, 2-phenylamino-9-[4-(1-decahydroquinolyl)butyl]-6-oxopurine (I·2 HCl), was a competitive inhibitor, with  $K_i$  values of 0.03 and 0.005  $\mu\text{M}$  against HSV-1 and HSV-2 TKs, resp. The parent compound HBPG was uniquely active in viral infection models in mice, both against ocular HSV-2 reactivation and against HSV-1 and HSV-2 encephalitis. In assays lacking [ $^3\text{H}$ ]thymidine, HBPG was found to be an efficient substrate for the enzymes. The ability of the TKs to phosphorylate HBPG may relate to its antiherpetic activity *in vivo*.

AN 2005:398777 HCPLUS <<LOGINID::20091212>>  
 DN 143:97319  
 TI Inhibition of Herpes Simplex Virus Thymidine Kinases by  
 2-Phenylamino-6-oxopurines and Related Compounds: Structure-Activity  
 Relationships and Antiherpetic Activity *in Vivo*  
 AU Manikowski, Andrzej; Verri, Annalisa; Lossani, Andrea; Gebhardt, Bryan M.;  
 Gambino, Joseph; Focher, Federico; Spadari, Silvio; Wright, George E.  
 CS GLSynthesis Inc., Worcester, MA, 01605, USA  
 SO Journal of Medicinal Chemistry (2005), 48(11), 3919-3929  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CASREACT 143:97319  
 IT 161363-19-5  
 RL: PAC (Pharmacological activity); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)  
 (inhibition of herpes simplex virus thymidine kinases by  
 2-phenylamino-6-oxopurines and related compds., structure-activity  
 relationships and antiherpetic activity *in vivo*)  
 RN 161363-19-5 HCPLUS  
 CN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(phenylamino)- (CA INDEX NAME)

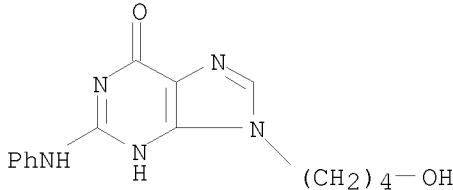


IT 856669-26-6P  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL  
 (Biological study); PREP (Preparation)  
 (inhibition of herpes simplex virus thymidine kinases by  
 2-phenylamino-6-oxopurines and related compds., structure-activity  
 relationships and antiherpetic activity *in vivo*)  
 RN 856669-26-6 HCPLUS  
 CN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(methylphenylamino)- (CA INDEX NAME)



OSC.G 14 THERE ARE 14 CAPLUS RECORDS THAT CITE THIS RECORD (14 CITINGS)  
 RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

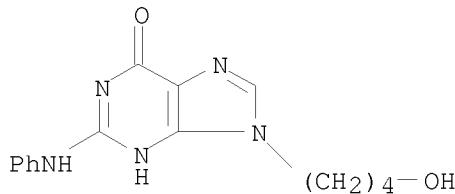
L4 ANSWER 3 OF 12 HCPLUS COPYRIGHT 2009 ACS on STN  
 TI Binding Mode Prediction of Cytochrome P450 and Thymidine Kinase Protein-Ligand Complexes by Consideration of Water and Rescoring in Automated Docking  
 AB The popular docking programs AutoDock, FlexX, and GOLD were used to predict binding modes of ligands in crystallog. complexes including x-ray water mols. or computationally predicted water mols. Isoenzymes of two different enzyme systems were used, namely cytochromes P 450 ( $n = 19$ ) and thymidine kinases ( $n = 19$ ) and three different "water" scenarios: i.e., docking (i) into water-free active sites, (ii) into active sites containing crystallog. water mols., and (iii) into active sites containing water mols. predicted by a novel approach based on the program GRID. Docking accuracies were determined in terms of the root-mean-square deviation (RMSD) accuracy and, newly defined, in terms of the ligand catalytic site prediction (CSP) accuracy. Consideration of both x-ray and predicted water mols. and the subsequent pooling and rescoring of all solns. (generated by all three docking programs) with the SCORE scoring function significantly improved the quality of prediction of the binding modes both in terms of RMSD and CSP accuracy.  
 AN 2005:134376 HCPLUS <<LOGINID::20091212>>  
 DN 142:366752  
 TI Binding Mode Prediction of Cytochrome P450 and Thymidine Kinase Protein-Ligand Complexes by Consideration of Water and Rescoring in Automated Docking  
 AU de Graaf, Chris; Pospisil, Pavel; Pos, Wouter; Folkers, Gerd; Vermeulen, Nico P. E.  
 CS Leiden/Amsterdam Center for Drug Research, Division of Molecular Toxicology, Vrije Universiteit Amsterdam, Amsterdam, 1081 HV, Neth.  
 SO Journal of Medicinal Chemistry (2005), 48(7), 2308-2318  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PB American Chemical Society  
 DT Journal  
 LA English  
 IT 161363-19-5  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (binding mode prediction of cytochrome P 450 and thymidine kinase protein-ligand complexes by consideration of water and rescoring in automated docking)  
 RN 161363-19-5 HCPLUS  
 CN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(phenylamino)- (CA INDEX NAME)



OSC.G 49 THERE ARE 49 CAPLUS RECORDS THAT CITE THIS RECORD (49 CITINGS)  
 RE.CNT 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN  
 TI Novel antiherpes drug combinations of Herpes simplex virus thymidine kinase inhibitors and antiherpes substances  
 AB Composition and methods are disclosed that include a synergistic combination of an inhibitor of Herpes simplex virus thymidine kinase, and an antiherpes substance. The effect of combination of 2-phenylamino-9-(4-hydroxybutyl)-6-oxopurine and foscarnet against HSV2 encephalitis in mice was examined  
 AN 2004:681513 HCAPLUS <<LOGINID::20091212>>  
 DN 141:185078  
 TI Novel antiherpes drug combinations of Herpes simplex virus thymidine kinase inhibitors and antiherpes substances  
 IN Wright, George E.  
 PA University of Massachusetts, USA  
 SO PCT Int. Appl., 22 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004069168	A2	20040819	WO 2004-US2427	20040129
	WO 2004069168	A3	20050915		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2514334	A1	20040819	CA 2004-2514334	20040129
	US 20040259832	A1	20041223	US 2004-767019	20040129
	EP 1594507	A2	20051116	EP 2004-706459	20040129
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRAI	US 2003-443519P	P	20030129		
	WO 2004-US2427	W	20040129		
IT	161363-19-5				
	RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)				
	(antiherpes drug combinations of Herpes simplex virus thymidine kinase inhibitors and antiherpes substances)				
RN	161363-19-5	HCAPLUS			
CN	6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(phenylamino)-			(CA INDEX NAME)	



RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN

TI The rational of catalytic activity of herpes simplex virus thymidine kinase. A combined biochemical and quantum chemical study

AB Most antiherpes therapies exploit the large substrate acceptance of herpes simplex virus type 1 thymidine kinase (TK HSV1) relative to the human isoenzyme. The enzyme selectively phosphorylates nucleoside analogs that can either inhibit viral DNA polymerase or cause toxic effects when incorporated into viral DNA. To relate structural properties of TKHSV1 ligands to their chemical reactivity we have carried out ab initio quantum chemical calcns. within the d. functional theory framework in combination with biochem. studies. Calcns. have focused on a set of ligands carrying a representative set of the large spectrum of sugar-mimicking moieties and for which structural information of the TKHSV1ligand complex is available. The κcat values of these ligands have been measured under the same exptl. conditions using an UV spectrophotometric assay. The calcns. point to the crucial role of elec. dipole moment of ligands and its interaction with the neg. charged residue Glu225. A striking correlation is found between the energetics associated with this interaction and the κcat values measured under homogeneous conditions. This finding uncovers a fundamental aspect of the mechanism governing substrate diversity and catalytic turnover and thus represents a significant step toward the rational design of novel and powerful prodrugs for antiviral and TKHSV1-linked suicide gene therapies.

AN 2001:457254 HCAPLUS <<LOGINID::20091212>>

DN 135:207324

TI The rational of catalytic activity of herpes simplex virus thymidine kinase. A combined biochemical and quantum chemical study

AU Sulpizi, Marialore; Schelling, Pierre; Folkers, Gerd; Carloni, Paolo; Scapozza, Leonardo

CS International School Advanced Studies, Scuola Internazionale Superiore Studi Aranzati, Trieste, 34013, Italy

SO Journal of Biological Chemistry (2001), 276(24), 21692-21697  
CODEN: JBCHA3; ISSN: 0021-9258

PB American Society for Biochemistry and Molecular Biology

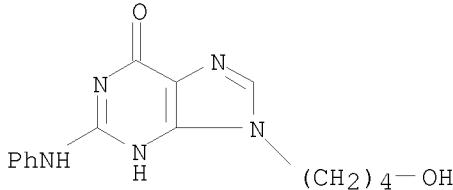
DT Journal

LA English

IT 161363-19-5  
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)  
(biochem. and quantum chemical study of nucleoside analogs interaction with herpes simplex virus thymidine kinase)

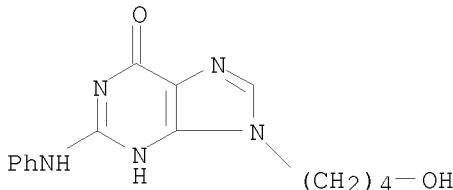
RN 161363-19-5 HCAPLUS

CN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(phenylamino)- (CA INDEX NAME)



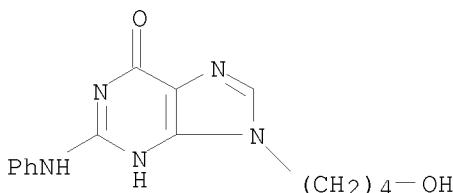
OSC.G 22 THERE ARE 22 CAPLUS RECORDS THAT CITE THIS RECORD (22 CITINGS)  
 RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN  
 TI Status of inhibitors of herpes simplex thymidine kinases  
 AB A review with 23 refs. Determination of the crystal structures of complexes of herpes simplex virus type 1 thymidine kinase (HSV1 TK) with its substrates has provided a detailed picture of the active site and an understanding of the wide substrate range of the enzyme. The binding mode of a class of nonsubstrate inhibitors, exemplified by 9-(4-hydroxybutyl)-N2-phenylguanine (HBPG), has been revealed in the crystal structure of the TK:HBPG complex, allowing rational design of improved inhibitors. Further studies of the effect of HBPG in a murine model of HSV1 latency demonstrated the promise of TK inhibitors in preventing reactivation of herpetic diseases.  
 AN 2000:34133 HCAPLUS <<LOGINID::20091212>>  
 DN 132:302785  
 TI Status of inhibitors of herpes simplex thymidine kinases  
 AU Wright, George E.; Gambino, Joseph J.; Sun, Hongmao; Gebhardt, Bryan M.  
 CS GL Synthesis Inc, Shrewsbury, MA, 01545, USA  
 SO Current Opinion in Anti-Infective Investigational Drugs (1999), 1(5), 541-546  
 CODEN: COADFY; ISSN: 1464-8458  
 PB Current Drugs Ltd.  
 DT Journal; General Review  
 LA English  
 IT 161363-19-5  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MSC (Miscellaneous); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (status of inhibitors of herpes simplex thymidine kinases, such as)  
 RN 161363-19-5 HCAPLUS  
 CN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(phenylamino)- (CA INDEX NAME)



OSC.G 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)  
 RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN  
 TI Structure to 1.9 Å resolution of a complex with herpes simplex virus type-1 thymidine kinase of a novel, non-substrate inhibitor: X-ray crystallographic comparison with binding of aciclovir  
 AB Treatment of herpes infections with nucleoside analogs requires as an initial step the activation of the compds. by thymidine kinase. As an aid to developing more effective chemotherapy, both for treatment of recurrent herpes infection and in gene therapy systems where thymidine kinase is expressed, two high-resolution X-ray structures of thymidine kinase have been compared: one with the relatively poor substrate aciclovir (Zovirax), the other with a synthetic inhibitor having an N2-substituted guanine (HBPG; 9-(4-hydroxybutyl)-N2-phenylguanine). Both compds. have similar binding modes in spite of their size difference and apparently distinct ligand properties.  
 AN 1999:60517 HCAPLUS <<LOGINID::20091212>>  
 DN 130:293191  
 TI Structure to 1.9 Å resolution of a complex with herpes simplex virus type-1 thymidine kinase of a novel, non-substrate inhibitor: X-ray crystallographic comparison with binding of aciclovir  
 AU Bennett, Matthew S.; Wien, Frank; Champness, John N.; Batuwangala, Thilina; Rutherford, Thomas; Summers, William C.; Sun, Hongmao; Wright, George; Sanderson, Mark R.  
 CS Randall Institute, Division of Biomedical Sciences, King's College, London, WC2B 5RL, UK  
 SO FEBS Letters (1999), 443(2), 121-125  
 CODEN: FEBLAL; ISSN: 0014-5793  
 PB Elsevier Science B.V.  
 DT Journal  
 LA English  
 IT 161363-19-5D, thymidine kinase complexes  
 RL: PRP (Properties)  
 (crystal structure to 1.9 Å resolution of a complex with herpes simplex virus type-1 thymidine kinase of a novel, non-substrate inhibitor and comparison with binding of aciclovir)  
 RN 161363-19-5 HCAPLUS  
 CN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(phenylamino)- (CA INDEX NAME)



OSC.G 38 THERE ARE 38 CAPLUS RECORDS THAT CITE THIS RECORD (38 CITINGS)  
 RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN  
 TI Phenylguanines and alkylguanines, their preparation, and their use for preventing recurrent herpes virus infections  
 AB N2-substituted alkylguanines and N2-substituted phenylguanines which prevent recurrent herpes simplex infections are disclosed. By virtue of their ability to inhibit herpes virus thymidine kinase in vivo, such compds. will prevent, reduce the frequency of, or reduce the severity of recurring HSV infections in humans. Preparation of

9-(2,3-dihydroxypropyl)-N2-phenylguanine and other guanine derivs. of the invention is described, as are pharmacokinetic parameters, and effect on viral reactivation and on varicella zoster thymidine kinase.

AN 1997:456147 HCPLUS <<LOGINID::20091212>>

DN 127:145171

OREF 127:27885a, 27888a

TI Phenylguanines and alkylguanines, their preparation, and their use for preventing recurrent herpes virus infections

IN Wright, George E.

PA University of Massachusetts Medical Center, USA

SO U.S., 15 pp., Cont.-in-part of U.S. Ser. No. 241,686, abandoned.  
CODEN: USXXAM

DT Patent

LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5646155	A	19970708	US 1994-365769	19941229
	WO 9620711	A1	19960711	WO 1995-US16873	19951228
	W: AU, CN, JP, KR RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE AU 9646886	A	19960724	AU 1996-46886	19951228
	EP 794781	A1	19970917	EP 1995-944530	19951228
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE JP 10511952	T	19981117	JP 1995-521119	19951228
PRAI	US 1994-241686	B2	19940512		
	US 1994-365769	A	19941229		
	WO 1995-US16873	W	19951228		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

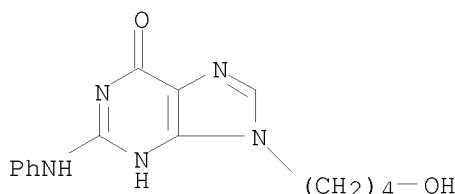
OS MARPAT 127:145171

IT 161363-19-5P

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)  
(phenylguanine and alkylguanine preparation and use for preventing recurrent herpes virus infections)

RN 161363-19-5 HCPLUS

CN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(phenylamino)- (CA INDEX NAME)



OSC.G 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

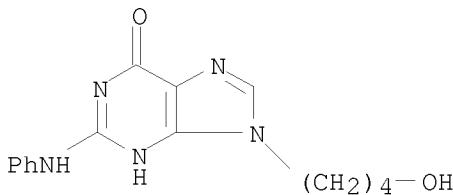
L4 ANSWER 9 OF 12 HCPLUS COPYRIGHT 2009 ACS on STN

TI Effect of 9-(4-hydroxybutyl)-N2-phenylguanine (HBPg), a thymidine kinase inhibitor, on clinical recurrences of ocular herpetic keratitis in squirrel monkeys

AB 9-(4-Hydroxybutyl)-N2-phenylguanine (HBPg) is a new viral thymidine kinase

inhibitor that we tested for the ability to prevent recurrences of herpetic keratitis. Eighteen squirrel monkeys (*Saimiri scuireus*) were infected in both corneas with the Rodanus strain of herpes simplex virus type 1 (HSV-1). All corneas showed typical dendritic keratitis 3 days after infection, followed by spontaneous healing. On day 21, the monkeys were randomized into two coded groups and ocular examns. were begun. One group received i.p. injections of HPG, 150 mg/kg, in a corn oil suspension every 8 h, and the other group received i.p. injections of the corn oil vehicle only. On day 22, recurrences were induced by reducing the temperature of the room in the late afternoon so that a low of 18° was achieved during the night. After the morning treatment, room temperature was raised to the normal ambient temperature (24-27°), and treatment was discontinued. Treatment was reinstated on day 27, the room temperature was lowered again on day 28, and treatment was again discontinued as before. Third and fourth cycles of treatment and cold stress were begun on days 34 and 69. Ocular examns. were continued until day 73, at which point the code was broken. We found that the HPG treatment significantly reduced the number of corneas with recurrences during the treatment periods, compared with recurrences in untreated, cold-stressed animals.

AN 1996:692561 HCPLUS <<LOGINID::20091212>>  
 DN 126:26411  
 OREF 126:5253a,5256a  
 TI Effect of 9-(4-hydroxybutyl)-N2-phenylguanine (HPG), a thymidine kinase inhibitor, on clinical recurrences of ocular herpetic keratitis in squirrel monkeys  
 AU Kaufman, Herbert E.; Varnell, Emily D.; Wright, George E.; Xu, Hongyan; Gebhardt, Bryan M.; Thompson, Hilary W.  
 CS Lions Eye Research Laboratories, LSU Eye Center, Louisiana State University Medical Center School of Medicine, New Orleans, LA, 70112, USA  
 SO Antiviral Research (1996), 33(1), 65-72  
 CODEN: ARSRDR; ISSN: 0166-3542  
 PB Elsevier  
 DT Journal  
 LA English  
 IT 161363-19-5  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (effect of 9-(4-hydroxybutyl)-N2-phenylguanine (HPG), a thymidine kinase inhibitor, on clin. recurrences of ocular herpetic keratitis in squirrel monkeys)  
 RN 161363-19-5 HCPLUS  
 CN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(phenylamino)- (CA INDEX NAME)



OSC.G 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)

L4 ANSWER 10 OF 12 HCPLUS COPYRIGHT 2009 ACS on STN  
 TI N2-Substituted alkylguanines and N2-substituted phenylguanines, and their preparation, to prevent recurrent herpes virus infections

AB N2-substituted alkylguanines and N2-substituted phenylguanine compds. which prevent recurrent herpes simplex infections are disclosed. By virtue of their ability to inhibit herpes virus thymidine kinase in vivo, such compds. will prevent, reduce the frequency of, or reduce the severity of recurrent HSV infections in humans. Preparation and activity of the compds. of the invention are described.

AN 1996:548529 HCAPLUS <<LOGINID::20091212>>

DN 125:185858

OREF 125:34538h,34539a

TI N2-Substituted alkylguanines and N2-substituted phenylguanines, and their preparation, to prevent recurrent herpes virus infections

IN Wright, George E.

PA University of Massachusetts Medical Center, USA

SO PCT Int. Appl., 40 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9620711	A1	19960711	WO 1995-US16873	19951228
	W: AU, CN, JP, KR RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 5646155	A	19970708	US 1994-365769	19941229
	AU 9646886	A	19960724	AU 1996-46886	19951228
	EP 794781	A1	19970917	EP 1995-944530	19951228
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 10511952	T	19981117	JP 1995-521119	19951228
PRAI	US 1994-365769	A	19941229		
	US 1994-241686	B2	19940512		
	WO 1995-US16873	W	19951228		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

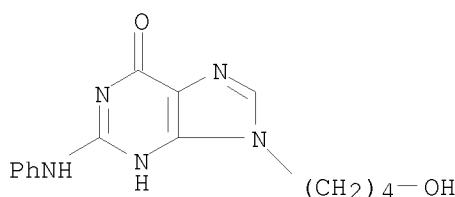
OS MARPAT 125:185858

IT 161363-19-5P

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)  
(alkylguanine and phenylguanine preparation for prevention of recurrent herpes virus infections)

RN 161363-19-5 HCAPLUS

CN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(phenylamino)- (CA INDEX NAME)



OSC.G 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

L4 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN

TI 9-(4-Hydroxybutyl)-N2-phenylguanine (HBPG), a thymidine kinase inhibitor, suppresses herpes virus reactivation in mice

AB In cells of the nervous system, which have little or no cellular thymidine

kinase, the pharmacol. inhibition of viral thymidine kinase may prevent the reactivation of herpes virus, which requires phosphorylated thymidine for replication. We tested a newly synthesized inhibitor of viral thymidine kinase, 9-(4-hydroxybutyl)-N2-phenylguanine (HBPg) for its capacity to suppress the reactivation of herpes simplex virus type 1 (HSV-1) in vivo. Mice, latently infected with McKrae strain HSV-1, were treated with i.p. injections of HBPg in a corn oil vehicle (200 mg/kg every 3 h for a total of ten doses), and subjected to hyperthermic stress to stimulate viral reactivation immediately before the third treatment. Three h after the last treatment, the mice were sacrificed, and the presence of infectious virus was determined by culture of ocular surface swabs and trigeminal ganglionic homogenates. Addnl., viral DNA in ganglionic exts. was analyzed by quant. PCR. Controls included latently infected, stressed animals receiving injections of corn oil vehicle only, and latently infected, drug- and vehicle-treated, unstressed animals. HBPg had a statistically significant inhibitory effect on hyperthermia-induced viral reactivation. Homogenates of trigeminal ganglia and ocular surface swabs from HBPg-treated animals were less likely to contain infectious virus than those of infected, vehicle-treated, stressed controls (ANOVA). Unstressed controls showed no reactivation. Quantitation of viral DNA in ganglionic exts. demonstrated a 100-fold reduction in the amount of viral DNA

in

the ganglia of HBPg-treated animals, compared with vehicle-treated controls (ANOVA). The results indicate that HBPg has an inhibitory effect when given systemically for the suppression of herpes virus reactivation in mice.

AN 1996:330473 HCPLUS <<LOGINID::20091212>>

DN 125:104317

OREF 125:19235a,19238a

TI 9-(4-Hydroxybutyl)-N2-phenylguanine (HBPg), a thymidine kinase inhibitor, suppresses herpes virus reactivation in mice

AU Gebhardt, Bryan M.; Wright, George E.; Xu, Hongyan; Focher, Federico; Spadari, Silvio; Kaufman, Herbert E.

CS Lions Eye Research Laboratories, LSU Eye Center, Louisiana State University Medical Center School of Medicine, New Orleans, LA, 70112, USA

SO Antiviral Research (1996), 30(2,3), 87-94

CODEN: ARSRDR; ISSN: 0166-3542

PB Elsevier

DT Journal

LA English

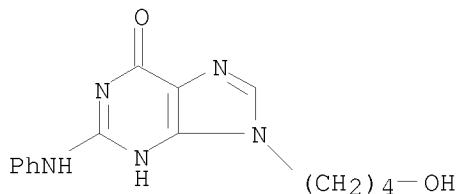
IT 161363-19-5

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(9-(4-Hydroxybutyl)-N2-phenylguanine (HBPg), a thymidine kinase inhibitor, suppresses herpes virus reactivation in mice)

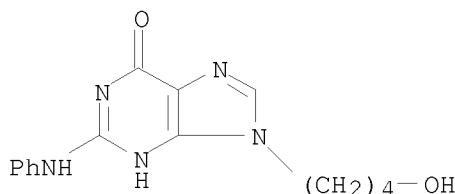
RN 161363-19-5 HCPLUS

CN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(phenylamino)- (CA INDEX NAME)



OSC.G 14 THERE ARE 14 CAPLUS RECORDS THAT CITE THIS RECORD (14 CITINGS)

L4 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN  
TI Synthesis, Properties, and Pharmacokinetic Studies of N2-Phenylguanine Derivatives as Inhibitors of Herpes Simplex Virus Thymidine Kinases  
AB Two series of selective inhibitors of herpes simplex virus types 1 and 2 (HSV1,2) thymidine kinases (TK) have been developed as a potential treatment for recurrent virus infections. Among compds. related to the potent base analog N2-[m-(trifluoromethyl)phenyl]guanine (mCF3PG), none was a more potent inhibitor than mCF3PG itself. Compds. related to the nucleoside N2-phenyl-2'-deoxyguanosine (PhdG), but with alkyl, hydroxyalkyl, and related substituents at the 9-position in place of the glycosyl group of PhdG, retained significant but variable inhibitory potencies against the HSV TKs. The most potent inhibitor of HSV1 TK among 9-substituted derivs., 9-(4-hydroxybutyl)-N2-phenylguanine (HBPg), was a competitive inhibitor with respect to the substrate thymidine but was not itself a substrate for the enzyme. Water solubilities and 1-octanol:water partition coeffs. for the 9-substituted N2-phenylguanines were linearly but oppositely related to the sum of hydrophobic fragmental consts. ( $\Sigma f$ ) of the 9-substituents. Four of the inhibitors were given as solns. to mice by i.v. and i.p. routes, and the time course of their plasma concns. was determined by HPLC anal. of the parent compds. HBPg was completely absorbed by the i.p. route, and the plasma concentration could be prolonged by use of suspension formulations. HBPg is a candidate for animal trials as a treatment for recurrent herpes virus infections.  
AN 1995:283758 HCAPLUS <<LOGINID::20091212>>  
DN 122:150822  
OREF 122:27641a, 27644a  
TI Synthesis, Properties, and Pharmacokinetic Studies of N2-Phenylguanine Derivatives as Inhibitors of Herpes Simplex Virus Thymidine Kinases  
AU Xu, Hongyan; Maga, Giovanni; Focher, Federico; Smith, Emil R.; Spadari, Silvio; Gambino, Joseph; Wright, George E.  
CS Medical School, University of Massachusetts, Worcester, MA, 01655, USA  
SO Journal of Medicinal Chemistry (1995), 38(1), 49-57  
CODEN: JMCMAR; ISSN: 0022-2623  
PB American Chemical Society  
DT Journal  
LA English  
OS CASREACT 122:150822  
IT 161363-19-5P  
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)  
    (synthesis, properties, and pharmacokinetic studies of N2-phenylguanine derivs. as inhibitors of herpes simplex virus thymidine kinases)  
RN 161363-19-5 HCAPLUS  
CN 6H-Purin-6-one, 1,9-dihydro-9-(4-hydroxybutyl)-2-(phenylamino)- (CA INDEX NAME)



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USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2009

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<http://www.cas.org/support/stngen/stndoc/properties.html>

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E2      1      ACYCLOVIR MONONITRATE/CN
E3      1 --> ACYCLOVIR MONOPHOSPHATE/CN
E4      1      ACYCLOVIR PALMITATE/CN
E5      1      ACYCLOVIR PHOSPHONATE/CN
E6      1      ACYCLOVIR SODIUM/CN
E7      1      ACYCLOVIR SODIUM SALT/CN
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E12     1      ACYCLOVIR-HAFNOCENE DICHLORIDE COPOLYMER/CN

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E4      1      GANCIDIN A/CN
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E7 1 GANCYCLOVIR NITRATE/CN  
E8 1 GAND/CN  
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E10 1 GANDAVENSIN B/CN  
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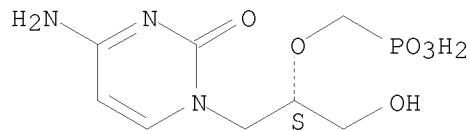
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E11 1 CIDOTEN/CN  
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=> d 12 scan

L2 1 ANSWERS REGISTRY COPYRIGHT 2009 ACS on STN  
IN Phosphonic acid, P-[[(1S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-  
(hydroxymethyl)ethoxy]methyl]-  
MF C8 H14 N3 O6 P  
CI COM

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

ALL ANSWERS HAVE BEEN SCANNED

=> exp foscarnet/cn

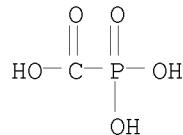
E1 1 FOSCARB/CN  
E2 1 FOSCARBOXIN/CN  
E3 1 --> FOSCARNET/CN  
E4 1 FOSCARNET SODIUM/CN  
E5 1 FOSCAVIR/CN  
E6 1 FOSCHLOR/CN  
E7 1 FOSCHLOR 50/CN  
E8 1 FOSCHLOR R/CN  
E9 1 FOSCHLOR R 50/CN  
E10 1 FOSCO 715/CN  
E11 1 FOSCOLIC ACID/CN  
E12 1 FOSDIOL/CN

=> s e3

L3 1 FOSCARNET/CN

=> d 13 scan

L3 1 ANSWERS REGISTRY COPYRIGHT 2009 ACS on STN  
IN Phosphinecarboxylic acid, 1,1-dihydroxy-, 1-oxide  
MF C H3 O5 P  
CI COM



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

ALL ANSWERS HAVE BEEN SCANNED

=> file hcaplus  
COST IN U.S. DOLLARS

SINCE FILE TOTAL  
ENTRY SESSION

FULL ESTIMATED COST

17.97

21.04

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USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2009

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=> s 11/thu or 12/thu or 13/thu  
    72 L1  
    1193460 THU/RL  
        17 L1/THU  
            (L1 (L) THU/RL)  
        960 L2  
    1193460 THU/RL  
        779 L2/THU  
            (L2 (L) THU/RL)  
        1209 L3  
    1193460 THU/RL  
        641 L3/THU  
            (L3 (L) THU/RL)  
L4        1216 L1/THU OR L2/THU OR L3/THU

=> s herpes  
L5        30155 HERPES

=> s 14 and 15  
L6        218 L4 AND L5

=> s 16 and (PY<2003 or AY<2003 or PRY<2003)  
    23001885 PY<2003  
    4531634 AY<2003  
    4001927 PRY<2003  
L7        128 L6 AND (PY<2003 OR AY<2003 OR PRY<2003)

=> s thymidine kinase

57757 THYMIDINE  
367259 KINASE  
L8 10740 THYMIDINE KINASE  
(THYMIDINE(W)KINASE)

=> s 17 and 18  
L9 21 L7 AND L8

=> d 19 1-21 ti abs bib

L9 ANSWER 1 OF 21 HCAPLUS COPYRIGHT 2009 ACS on STN  
TI Novel mutations in the thymidine kinase and DNA polymerase genes of acyclovir and foscarnet resistant herpes simplex viruses infecting an immunocompromised patient  
AB Background: Mutations in the thymidine kinase (TK) and DNA polymerase (pol) genes of herpes simplex virus (HSV) may confer resistance to antiviral drugs, particularly in the context of immunosuppression induced by infection with the human immunodeficiency virus (HIV). Objectives: To characterize the HSV type 2 (HSV-2) TK and DNA pol genes in an immunocompromised patient with clin. resistance to both acyclovir and foscarnet. Study design: The TK and DNA pol genes of isolates obtained over a 2-yr period from an AIDS patient with severe genital herpes infection were characterized both phenotypically and genotypically. Results: HSV strains that were acyclovir resistant/foscarnet sensitive, acyclovir sensitive/foscarnet sensitive and acyclovir resistant/foscarnet resistant were isolated during this time. The TK gene of all the acyclovir resistant isolates contained a large 969 bp deletion which extended into a downstream untranslated region. The foscarnet resistance was associated with an S725G mutation in a conserved region (region II) of the herpesvirus DNA pol gene. Conclusions: Clin. and virol. suppression of the infection was not always associated with subsequent reactivation with wild-type virus. Mutations of the nature we describe have not previously been reported occurring simultaneously in HSV strains isolated from patients treated with acyclovir and foscarnet.

AN 2002:742377 HCAPLUS <>LOGINID::20091214>

DN 138:232521

TI Novel mutations in the thymidine kinase and DNA polymerase genes of acyclovir and foscarnet resistant herpes simplex viruses infecting an immunocompromised patient

AU Chibo, Doris; Mijch, Anne; Doherty, Richard; Birch, Christopher

CS North Melbourne, Victorian Infectious Diseases Reference Laboratory, Melbourne, 3051, Australia

SO Journal of Clinical Virology (2002), 25(2), 165-170

CODEN: JCVIFB; ISSN: 1386-6532

PB Elsevier Science Ltd.

DT Journal

LA English

OSC.G 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)

RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 21 HCAPLUS COPYRIGHT 2009 ACS on STN  
TI Establishment and use of a cell line expressing HSV-1 thymidine kinase to characterize viral thymidine kinase -dependent drug-resistance  
AB To understand the mechanisms of antiviral drug resistance and to have a system to examine the cytotoxicity of herpes simplex virus type 1 (HSV-1) inhibitors that are thymidine kinase (TK)-dependent, the authors have constructed a plasmid pFTK1 by inserting a DNA fragment containing the TK gene of HSV-1 strain F into the eukaryotic expression vector pcDNA3.1/His A. TK-deficient 143B cells were transfected

with this vector and neomycin-resistant cells were selected. Cell survival in HAT medium and TK activity of the cell lysates were examined to ascertain HSV-1 TK expression. A cell line expressing the viral TK gene, FTK143B (FTK), was established and used for characterization of two laboratory-derived TK-deficient drug-resistant HSV-1 mutants of strain F. The antiviral activities of several drugs, mostly nucleoside analogs, were compared in the Vero, 143B and FTK cell culture systems. The authors showed that both mutant viruses lost their resistance to acyclovir and to other HSV-1 TK-dependent compds. in FTK cells but not in Vero and 143B cells. Significantly increased cytotoxicity of ganciclovir and (E)-5-(2-bromovinyl)-2'-deoxyuridine was also observed in the FTK cells. This HSV-1 TK gene-transfected cell model is a useful tool to rapidly determine HSV-1 drug resistance at the viral TK level.

AN 2002:300235 HCAPLUS <<LOGINID::20091214>>  
DN 137:362546  
TI Establishment and use of a cell line expressing HSV-1 thymidine kinase to characterize viral thymidine kinase -dependent drug-resistance  
AU Kim, Jee Hyun; Park, Jong Beak; Bae, Pan Kee; Kim, Hae Soo; Kim, Do Wan; Ahn, Jeong Keun; Lee, Chong-Kyo  
CS Pharmaceutical Screening Center, Korea Research Institute of Chemical Technology, Taejon, 305-600, S. Korea  
SO Antiviral Research (2002), 54(3), 163-174  
CODEN: ARSRDR; ISSN: 0166-3542  
PB Elsevier Science B.V.  
DT Journal  
LA English  
OSC.G 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)  
RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 21 HCAPLUS COPYRIGHT 2009 ACS on STN  
TI Antiviral activity of cyclosaligenyl prodrugs of acyclovir, carbovir, and abacavir  
AB The cyclosaligenyl (cycloSal) derivs. of the monophosphates of 3 acyclic or carbocyclic guanosine analogs, for example, acyclovir (ACV), carbovir (CBV), and abacavir (ABC), were investigated for their activity against retrovirus (HIV, Moloney sarcoma virus) and herpes simplex virus (HSV) activity in cell culture. The extent of the antiviral potency of the prodrugs depended on the nature of the nucleoside, the substituent on the cycloSal moiety and the virus investigated. Most notably, and unlike the parent compound ACV, cycloSal-ACV monophosphate (MP) prodrugs retained pronounced activity against ACV-resistant (thymidine kinase-deficient) HSV-1 and also gained anti-HIV activity. While the cycloSal-CBVMP prodrugs did not show enhanced activity compared with the parent compound CBV, the cycloSal-ABCMP prodrugs afforded markedly increased potency against both HSV and HIV. The authors' data indicate that the cycloSal prodrug approach can be useful to deliver directly the MP derivs. of nucleoside analogs into the intact, virus-infected cells, thus improving and extending the antiviral potency and spectrum of the drugs against retro- and herpesvirus strains.

AN 2002:153908 HCAPLUS <<LOGINID::20091214>>  
DN 137:338  
TI Antiviral activity of cyclosaligenyl prodrugs of acyclovir, carbovir, and abacavir  
AU Balzarini, Jan; Haller-Meier, Friederike; De Clercq, Erik; Meier, Chris  
CS Rega Institute for Medical Research, KU Leuven, Louvain, Belg.  
SO Antiviral Chemistry & Chemotherapy (2001), 12(5), 301-306  
CODEN: ACCHEH; ISSN: 0956-3202  
PB International Medical Press  
DT Journal

LA English  
OSC.G 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)  
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 21 HCAPLUS COPYRIGHT 2009 ACS on STN  
TI Biochemical characterization of a virus isolate, recovered from a patient with herpes keratitis, that was clinically resistant to acyclovir  
AB In vitro susceptibility assays of herpes simplex virus (HSV) do not necessarily correlate with treatment outcome. An HSV type 1 (HSV-1) isolate, N4, recovered from a patient who presented with herpes keratitis with localized immunosuppression, was characterized for susceptibility. Although the 50% inhibitory concentration (IC50) for this isolate was less than the accepted breakpoint for defining resistance to acyclovir ( $>2.0 \mu\text{g/mL}$ ), the following lines of evidence suggest that the isolate was acyclovir resistant: (1) the clin. history confirmed that the infection was nonresponsive to acyclovir; (2) the in vitro susceptibility was similar to that of a thymidine kinase (TK)-neg., acyclovir-resistant virus SLU360; (3) the IC50 of acyclovir was more than 10 times the IC50 for an acyclovir-susceptible control strain; (4) plaque-purified clonal isolates were resistant to acyclovir (IC50s,  $>2.0 \mu\text{g/mL}$ ); and (5) biochem. studies indicated that the HSV-1 N4 TK was partially impaired for acyclovir phosphorylation. Although residue changes were found in both the viral tk and pol coding regions of HSV-1 N4, characterization of a recombinant virus expressing the HSV-1 N4 polymerase suggested that the TK and Pol together conferred the acyclovir-resistance phenotype.

AN 2002:93183 HCAPLUS <<LOGINID::20091214>>

DN 137:163349

TI Biochemical characterization of a virus isolate, recovered from a patient with herpes keratitis, that was clinically resistant to acyclovir

AU Sarisky, Robert T.; Cano, Rachel; Nguyen, Tammy T.; Wittrock, Robert J.; Duffy, Karen E.; Clark, Phil; Bartus, Joan O.; Bacon, Teresa H.; Caspers-Velu, Laure; Hodinka, Richard L.; Leary, Jeffry J.

CS Department of Host Defense, Antimicrobial and Host Defense Ctr. of Excellence for Drug Discovery, GiaxoSmthKline Pharmaceuticals, Collegeville, PA, 19426-0989, USA

SO Clinical Infectious Diseases (2001), 33(12), 2034-2039  
CODEN: CIDIEL; ISSN: 1058-4838

PB University of Chicago Press

DT Journal

LA English

OSC.G 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 21 HCAPLUS COPYRIGHT 2009 ACS on STN  
TI Infection due to aciclovir resistant herpes simplex virus in patients undergoing allogeneic hematopoietic stem cell transplantation  
AB Over an 8-mo period from Oct. 1997 to May 1998, 4 patients who had received bone marrow transplant (BMT) from unrelated donor presented with severe mucosal cutaneous infections involving aciclovir resistant herpes simplex virus 1 (HSV-1). The 4 isolates were aciclovir (ACV) resistant, 3 of which were also foscarnet resistant as determined by the dye uptake method. The sequencing of the thymidine kinase (TK) gene did not permit to establish a relation between mutations and resistance to ACV. 3 Patients were considered as clin. cured of their HSV infection by replacement of ACV or foscarnet with either valaciclovir (1 case) or cidofovir (two cases) but eventually 2 of

them died of graft vs host disease. 1 Patient died of extensive HSV infection despite administration of cidofovir. This study emphasizes the importance of monitoring the herpes virus resistance to antiviral drugs in bone marrow transplant recipients and the usefulness of the evaluation of novel antiviral drug for treatment of infections due to strains of HSV resistant to ACV and foscarnet that occur in about 5% of immunocompromised patients.

AN 2001:825249 HCPLUS <>LOGINID::20091214>>  
DN 136:318855  
TI Infection due to aciclovir resistant herpes simplex virus in patients undergoing allogeneic hematopoietic stem cell transplantation  
AU Venard, V.; Dauendorffer, J. N.; Carret, A. S.; Corsaro, D.; Edert, D.; Bordigoni, P.; Le Faou, A.  
CS Unite mixte de recherche 7565 UHP-CNRS, laboratoire de bacteriologie-virologie, faculte de medecine, Vandoeuvre-les-Nancy, Fr.  
SO Pathologie Biologie (2001), 49(7), 553-558  
CODEN: PTBIAN; ISSN: 0031-3009  
PB Editions Scientifiques et Medicales Elsevier  
DT Journal  
LA English  
OSC.G 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)  
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 21 HCPLUS COPYRIGHT 2009 ACS on STN  
TI Hydroxyurea potentiates the antiherpesvirus activities of purine and pyrimidine nucleoside and nucleoside phosphonate analogs  
AB Hydroxyurea has been shown to potentiate the anti-human immunodeficiency virus activities of 2',3'-dideoxynucleoside analogs such as didanosine. We have now evaluated in vitro the effect of hydroxyurea on the antiherpesvirus activities of several nucleoside analogs (acyclovir [ACV], ganciclovir [GCV], penciclovir [PCV], lobucavir [LBV], (R)-9-[4-hydroxy-2-(hydroxymethyl)butyl]guanine [H2G], and brivudin and nucleoside phosphonate analogs (cidofovir [CDV] and adefovir [ADV]). When evaluated in cytopathic effect (CPE) reduction assays, hydroxyurea by itself had little effect on CPE progression and potentiated in a subsynergistic (herpes simplex virus type 1 [HSV-1]) to synergistic (HSV-2) fashion the antiviral activities of ACV, GCV, PCV, LBV, H2G, ADV, and CDV. Hydroxyurea also caused marked increases in the activities of ACV, GCV, PCV, LBV, and H2G (compds. that depend for their activation on a virus-encoded thymidine kinase [TK]) against TK-deficient (TK-) HSV-1. In fact, in combination with hydroxyurea the 50% effective concns. of these compds. for inhibition of TK- HSV-1-induced CPE decreased from values of 20 to  $\geq$ 100  $\mu$ g/mL (in the absence of hydroxyurea) to values of 1 to 5  $\mu$ g/mL (in the presence of hydroxyurea at 25 to 100  $\mu$ g/mL). When evaluated in a single-cycle virus yield reduction assay, hydroxyurea at a concentration of 100  $\mu$ g/mL inhibited progeny virus production by 60 to 90% but had little effect on virus yield at a concentration of 25  $\mu$ g/mL. Under these assay conditions hydroxyurea still elicited a marked potentiating effect on the antiherpesvirus activities of GCV and CDV, but this effect was less pronounced than that in the CPE reduction assay. It is conceivable that the potentiating effect of hydroxyurea stems from a depletion of the intracellular deoxynucleoside triphosphate pools, thus favoring the triphosphates of the nucleoside analogs (or the diphosphates of the nucleoside phosphonate analogs) in their competition with the natural nucleotides at the viral DNA polymerase level. The possible clin. implications of these findings are discussed.

AN 1999:784932 HCPLUS <>LOGINID::20091214>>  
DN 132:117100  
TI Hydroxyurea potentiates the antiherpesvirus activities of purine and

AU pyrimidine nucleoside and nucleoside phosphonate analogs  
AU Neyts, J.; De Clercq, E.  
CS Rega Institute for Medical Research, Louvain, B-3000, Belg.  
SO Antimicrobial Agents and Chemotherapy (1999), 43(12), 2885-2892  
CODEN: AMACCQ; ISSN: 0066-4804  
PB American Society for Microbiology  
DT Journal  
LA English  
OSC.G 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)  
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 21 HCPLUS COPYRIGHT 2009 ACS on STN  
TI Characterization of the DNA polymerase and thymidine kinase genes of herpes simplex virus isolates from AIDS patients in whom acyclovir and foscarnet therapy sequentially failed  
AB Herpes simplex virus (HSV) isolates were characterized from 8 AIDS patients in whom acyclovir and foscarnet therapy sequentially failed. The 6 postacyclovir (prefoscarnet) HSV isolates were resistant to acyclovir and susceptible to foscarnet. Of the 9 postfoscarnet isolates, 8 were foscarnet-resistant and acyclovir-susceptible, 1 was resistant to both drugs. Acyclovir or foscarnet-resistant isolates retained susceptibility to cidofovir. The acyclovir-resistant isolates contained single-base substitutions or frameshift mutations in G or C homopolymer nucleotide repeats of the thymidine kinase gene. In contrast, the foscarnet-resistant strains contained single-base substitutions in conserved (II, III, or VI) or, more rarely, nonconserved (between I and VII) regions of the DNA polymerase (pol) gene. The single isolate exhibiting resistance to acyclovir and foscarnet contained mutations in both genes. In this study of clin. HSV isolates, DNA pol mutations conferring foscarnet resistance were not associated with decreased acyclovir or cidofovir susceptibility.

AN 1999:528343 HCPLUS <>LOGINID::20091214>>  
DN 132:87784  
TI Characterization of the DNA polymerase and thymidine kinase genes of herpes simplex virus isolates from AIDS patients in whom acyclovir and foscarnet therapy sequentially failed  
AU Schmit, Isabelle; Boivin, Guy  
CS Infectious Disease Research Center, Centre Hospitalier de l'Universite Laval, Quebec City, QC, Can.  
SO Journal of Infectious Diseases (1999), 180(2), 487-490  
CODEN: JIDIAQ; ISSN: 0022-1899  
PB University of Chicago Press  
DT Journal  
LA English  
OSC.G 31 THERE ARE 31 CAPLUS RECORDS THAT CITE THIS RECORD (31 CITINGS)  
RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 21 HCPLUS COPYRIGHT 2009 ACS on STN  
TI Nucleoside analog phosphates for topical use in the treatment of herpes virus infections  
AB Compns. for topical use in herpes virus infections comprise anti-herpes nucleoside analog phosphate esters, e.g. acyclovir monophosphate, acyclovir diphosphate, and acyclovir triphosphate which show increased activity against native strains of herpes virus as well as against resistant strains, particularly thymidine kinase neg. strains of virus. Also disclosed are methods for treatment of herpes infections with nucleoside phosphates. Anti-herpes nucleoside analogs phosphate esters include the phosphoramidates and phosphothiorates, as well as polyphosphates

comprising C and S bridging atoms.  
 AN 1999:175589 HCAPLUS <<LOGINID::20091214>>  
 DN 130:218263  
 TI Nucleoside analog phosphates for topical use in the treatment of herpes virus infections  
 IN Hostetler, Karl Y.  
 PA USA  
 SO U.S., 19 pp., Cont.-in-part of U.S. 5,580,571.  
 CODEN: USXXAM  
 DT Patent  
 LA English  
 FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5879700	A	19990309	US 1995-480456	19950607 <--
	US 5580571	A	19961203	US 1993-60258	19930512 <--
	CA 2222154	A1	19961219	CA 1996-2222154	19960606 <--
	WO 9640088	A1	19961219	WO 1996-US10085	19960606 <--
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
	AU 9663842	A	19961230	AU 1996-63842	19960606 <--
	EP 831794	A1	19980401	EP 1996-923289	19960606 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	CN 1192138	A	19980902	CN 1996-195922	19960606 <--
	JP 11507642	T	19990706	JP 1997-502194	19960606 <--
	CN 1221609	A	19990707	CN 1998-123863	19981030 <--
PRAI	US 1991-777683	B2	19911015	<--	
	US 1993-60258	A2	19930512	<--	
	US 1995-480456	A	19950607	<--	
	WO 1996-US10085	W	19960606	<--	

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 9 OF 21 HCAPLUS COPYRIGHT 2009 ACS on STN  
 TI Mode of action of (1'S,2'R)-9-[1',2'-bis(hydroxymethyl)cycloprop-1'-yl]methyl}guanine (A-5021) against herpes simplex virus Type 1 and Type 2 and varicella-zoster virus  
 AB The mode of action of (1'S,2'R)-9-[1',2'-bis(hydroxymethyl)cycloprop-1'-yl]methyl}guanine (A-5021) against herpes simplex virus type 1 (HSV-1), HSV-2, and varicella-zoster virus (VZV) was studied. A-5021 was monophosphorylated at the 2' site by viral thymidine kinases (TKs). The 50% inhibitory values for thymidine phosphorylation of A-5021 by HSV-1 TK and HSV-2 TK were comparable to those for penciclovir (PCV) and lower than those for acyclovir (ACV). Of these three agents, A-5021 inhibited VZV TK most efficiently. A-5021 was phosphorylated to a mono-, di-, and triphosphate in MRC-5 cells infected with HSV-1, HSV-2, and VZV. A-5021 triphosphate accumulated more than ACV triphosphate but less than PCV triphosphate in MRC-5 cells infected with HSV-1 or VZV, whereas HSV-2-infected MRC-5 cells had comparable levels of A-5021 and ACV triphosphates. The intracellular half-life of A-5021 triphosphate was considerably longer than that of ACV triphosphate and shorter than that of PCV triphosphate. A-5021 triphosphate competitively inhibited HSV DNA polymerases with respect to dGTP. Inhibition was strongest with ACV triphosphate, followed by A-5021 triphosphate and then (R,S)-PCV triphosphate. A DNA chain elongation experiment revealed that A-5021 triphosphate was incorporated into DNA instead of dGTP and terminated

elongation, although limited chain extension was observed. Thus, the strong antiviral activity of A-5021 appears to depend on a more rapid and stable accumulation of its triphosphate in infected cells than that of ACV and on stronger inhibition of viral DNA polymerase by its triphosphate than that of PCV.

AN 1998:516837 HCAPLUS <<LOGINID::20091214>>  
DN 129:239501  
OREF 129:48571a,48574a  
TI Mode of action of (1'S,2'R)-9-{[1',2'-bis(hydroxymethyl)cycloprop-1'-yl]methyl}guanine (A-5021) against herpes simplex virus Type 1 and Type 2 and varicella-zoster virus  
AU Ono, Nobukazu; Iwayama, Satoshi; Suzuki, Katsuya; Sekiyama, Takaaki; Nakazawa, Harumi; Tsuji, Takashi; Okunishi, Masahiko; Daikoku, Tohru; Nishiyama, Yukihiro  
CS Life Science Laboratories, Ajinomoto Co., Inc., Yokohama, 244, Japan  
SO Antimicrobial Agents and Chemotherapy (1998), 42(8), 2095-2102  
CODEN: AMACQ; ISSN: 0066-4804  
PB American Society for Microbiology  
DT Journal  
LA English  
OSC.G 18 THERE ARE 18 CAPLUS RECORDS THAT CITE THIS RECORD (18 CITINGS)  
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 10 OF 21 HCAPLUS COPYRIGHT 2009 ACS on STN  
TI Compositions comprising an inducing agent and an antiviral agent for the treatment of blood, viral and cellular disorders  
AB Compns. and methods are provided for administration to a patient or to cells in vitro for the treatment of human disorders. In one embodiment, compns. contain chemical compds. that stimulate the expression of fetal Hb and/or stimulate the proliferation of red blood cells, white blood cells and platelets in patients and ex vivo for reconstitution of hematopoiesis in vivo. These methods are useful to treat or prevent the symptoms associated with anemia, sickle cell disease, thalassemia and other blood disorders. In another embodiment, compns. contain an inducing agent and an antiviral agent. The inducing agent induces the expression of a cellular or viral product, such as viral thymidine kinase, increasing the sensitivity of proliferating cells to the antiviral agent. Typical antiviral agents include nucleoside analogs, e.g. ganciclovir, that inhibit viral replication. Methods involve administration of therapeutically effective amts. of the inducing agent with the antiviral agent to destroy virus-infected cells. Viral infections that can be treated include infections by herpes viruses (e.g. Kaposi's-associated herpes virus) and Epstein-Barr virus, HIV infections, and HTLV infections. These compns. and methods are particularly effective against episomal and latent infections in proliferating cells. Also provided are methods for the pulsed administration of compns. to patients for the treatment and prevention of cell proliferative disorders, including deficiencies (e.g. cytopenia) and malignancies (e.g. such as viral-induced tumors), other forms of neoplasia, and for expansion of cells for hematopoietic transplantation.

AN 1998:98348 HCAPLUS <<LOGINID::20091214>>  
DN 128:176175  
OREF 128:34599a,34602a  
TI Compositions comprising an inducing agent and an antiviral agent for the treatment of blood, viral and cellular disorders  
IN Perrine, Susan P.; Faller, Douglas V.; White, Brian F.  
PA Perrine, Susan P., USA; Faller, Douglas V.; White, Brian F.  
SO PCT Int. Appl., 136 pp.  
CODEN: PIXXD2  
DT Patent

LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9804290	A2	19980205	WO 1997-US12818	19970728 <--
	WO 9804290	A3	19980813		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5939456	A	19990817	US 1996-687670	19960726 <--
	CA 2263675	A1	19980205	CA 1997-2263675	19970728 <--
	AU 9738891	A	19980220	AU 1997-38891	19970728 <--
	EP 969869	A2	200000112	EP 1997-936153	19970728 <--
	R: BE, CH, DE, FR, GB, GR, IT, LI				
	JP 2001527517	T	20011225	JP 1998-508931	19970728 <--
	EP 1611885	A1	20060104	EP 2005-12584	19970728 <--
	R: BE, CH, DE, FR, GB, GR, IT, LI				
	EP 1886677	A1	20080213	EP 2007-14281	19970728 <--
	R: BE, CH, DE, FR, GB, GR, IT, LI				
	US 20010009922	A1	20010726	US 2001-756489	20010108 <--
	US 6677302	B2	20040113		
PRAI	US 1996-687670	A	19960726	<--	
	US 1996-687671	A	19960726	<--	
	EP 1997-936153	A3	19970728	<--	
	EP 2005-12584	A3	19970728	<--	
	WO 1997-US12818	W	19970728	<--	

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OS MARPAT 128:176175

OSC.G 12 THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (15 CITINGS)

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 21 HCPLUS COPYRIGHT 2009 ACS on STN

TI Penciclovir and pathogenesis phenotypes of drug-resistant Herpes simplex virus mutants

AB The authors compared the penciclovir susceptibilities and pathogenesis phenotypes of mutants of Herpes simplex virus type 1 that are resistant to acyclovir and/or foscarnet. The mutants, which were derived from laboratory strain KOS, included six DNA polymerase mutants, a thymidine kinase neg. mutant, a thymidine kinase partial mutant, and a double mutant. Two of four polymerase mutants not previously examined for penciclovir susceptibility exhibited modest resistance to this drug. A thymidine kinase neg. mutant exhibited .apprx.20-fold resistance while a thymidine kinase partial mutant was penciclovir-sensitive. Following intracerebral inoculation of 7-wk old CD1 mice, the mutants ranged from exhibiting near wild-type neurovirulence (thymidine kinase partial) to modest attenuation (e.g. thymidine kinase neg.) to more severe attenuation.

Following corneal inoculation, three polymerase mutants exhibited modest deficits (relative to those of thymidine kinase neg.

mutants) in their abilities to replicate acutely in the ganglion and reactivate from latency. For mutant AraArl3, the deficit in ganglionic replication was shown to be due to its polymerase mutation by anal. of recombinant viruses derived by marker rescue. These results may have implications for issues of penciclovir action and resistance, for drug resistance in the clinic, and for the interactions of herpes

viruses with the peripheral and central nervous systems.  
AN 1998:72880 HCPLUS <<LOGINID::20091214>>  
DN 128:225719  
OREF 128:44557a  
TI Penciclovir and pathogenesis phenotypes of drug-resistant Herpes simplex virus mutants  
AU Pelosi, Emanuela; Mulamba, Gilbert B.; Coen, Donald M.  
CS Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA, 02115, USA  
SO Antiviral Research (1998), 37(1), 17-28  
CODEN: ARSRDR; ISSN: 0166-3542  
PB Elsevier Science B.V.  
DT Journal  
LA English  
OSC.G 27 THERE ARE 27 CAPLUS RECORDS THAT CITE THIS RECORD (27 CITINGS)  
RE.CNT 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 12 OF 21 HCPLUS COPYRIGHT 2009 ACS on STN  
TI Nucleosides and foscarnet-mechanisms  
AB A review with 76 refs. on basic mechanisms of drug resistance to herpes simplex virus types 1 and 2 and varicella zoster virus beginning with the nucleoside acyclovir and finishing with the pyrophosphate analog foscarnet. In the case of these viruses, these principles are illustrated by 2 kinds of drug targets; a deoxypyrimidine kinase, usually known as thymidine kinase, and the catalytic subunit of a viral DNA polymerase. Other viral target gene products that affect drug susceptibility are also discussed.  
AN 1997:567309 HCPLUS <<LOGINID::20091214>>  
DN 127:229082  
OREF 127:44507a, 44510a  
TI Nucleosides and foscarnet-mechanisms  
AU Coen, Donald M.  
CS Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA, 02115, USA  
SO Antiviral Drug Resistance (1996), 81-102. Editor(s): Richman, Douglas D. Publisher: Wiley, Chichester, UK.  
CODEN: 64XZAM  
DT Conference; General Review  
LA English  
OSC.G 13 THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (13 CITINGS)

L9 ANSWER 13 OF 21 HCPLUS COPYRIGHT 2009 ACS on STN  
TI Effect of foscarnet on experimental mouse model infected by acyclovir-resistant herpes simplex virus type 2  
AB Foscarnet (PFA) is a viral DNA polymerase inhibitor and has been used in the treatment of acyclovir-resistant herpes simplex virus (HSV) infection, but the study of PFA in the infected animals is fairly less than that of acyclovir (ACV), and the mechanism of HSV spread in the infected animals is not clear yet. We studied the virus spread and mortality following i.p. inoculation of HSV-2 RK (an acyclovir-resistant recombinant virus with altered thymidine kinase activity) while comparing to its parent virus 8620K. Neither the 50% LD (LD50) nor the average survival time was significantly different between the two virus strains. Parenteral ACV treatment was found to be effective against 8620K but not RK infection. Parenteral PFA treatment was effective against both RK and 8620K, and also inhibited spread of either virus to the liver, the spinal cord and the brain. Peroral PFA administration was found to prevent the virus replication in the liver.  
AN 1997:415987 HCPLUS <<LOGINID::20091214>>  
DN 127:60248

OREF 127:11337a, 11340a  
TI Effect of foscarnet on experimental mouse model infected by acyclovir-resistant herpes simplex virus type 2  
AU Li, Yuyu; Jin, Jinfu; Minagawa, Hirogo; Tanaka, S.; Mari, R.  
CS Yanbian Medical College, Yanji, 133000, Peop. Rep. China  
SO Zhonghua Shiyan He Linchuang Bingduxue Zazhi (1996), 10(2), 182-183  
CODEN: ZSLZFS; ISSN: 1003-9279  
PB Weishengbu Wuhan Shengwu Zhipin Yanjiuso  
DT Journal  
LA Chinese

L9 ANSWER 14 OF 21 HCPLUS COPYRIGHT 2009 ACS on STN  
TI Acyclovir derivatives for topical use  
AB The invention involves compns. for topical use in herpes virus infections comprising anti-herpes nucleoside analog phosphate esters, such as acyclovir monophosphate, acyclovir diphosphate, and acyclovir triphosphate, which show increased activity against native strains of herpes virus as well as against resistant strains, particularly thymidine kinase neg. strains of virus. Anti-herpes nucleoside analogs phosphate esters include the phosphoramidates and phosphothiorates, as well as polyphosphates comprising C and S bridging atoms.

AN 1997:121416 HCPLUS <>LOGINID::20091214>>  
DN 126:135594

OREF 126:26139a, 26142a  
TI Acyclovir derivatives for topical use  
IN Hostetler, Karl Y.  
PA Hostetler, Karl Y., USA  
SO PCT Int. Appl., 34 pp.  
CODEN: PIXXD2

DT Patent  
LA English

FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9640088	A1	19961219	WO 1996-US10085	19960606 <--
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
	US 5879700	A	19990309	US 1995-480456	19950607 <--
	AU 9663842	A	19961230	AU 1996-63842	19960606 <--
	EP 831794	A1	19980401	EP 1996-923289	19960606 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 11507642	T	19990706	JP 1997-502194	19960606 <--
PRAI	US 1995-480456	A	19950607	<--	
	US 1991-777683	B2	19911015	<--	
	US 1993-60258	A2	19930512	<--	
	WO 1996-US10085	W	19960606	<--	
OSC.G	3	THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)			
RE.CNT	2	THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD			
		ALL CITATIONS AVAILABLE IN THE RE FORMAT			

L9 ANSWER 15 OF 21 HCPLUS COPYRIGHT 2009 ACS on STN  
TI Nucleoside analogs for topical use in herpesvirus infections  
AB Compns. for topical use in herpesvirus infections comprise anti-herpes nucleoside analog phosphate esters, such as acyclovir

monophosphate and acyclovir diphosphate, which show increased activity against native strains of herpesvirus as well as against resistant strains, particularly thymidine kinase-neg. strains of the virus. Thus, acyclovir monophosphate was more effective than acyclovir in treatment of lesions in mice infected with an acyclovir-resistant strain of herpes simplex virus type 1. Acyclovir monophosphate was prepared by reaction of acyclovir with POCl<sub>3</sub> in P(O)(OMe)<sub>3</sub> followed by neutralization with aqueous NaOH.

AN 1996:754377 HCAPLUS <<LOGINID::20091214>>

DN 126:70124

OREF 126:13441a,13444a

TI Nucleoside analogs for topical use in herpesvirus infections

IN Hostetler, Karl Y.

PA Hostetler, Karl Y., USA

SO U.S., 14 pp., Cont.-in-part of U.S. Ser. No. 777,683, abandoned.

CODEN: USXXAM

DT Patent

LA English

FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5580571	A	19961203	US 1993-60258	19930512 <--
	US 5654286	A	19970805	US 1995-485025	19950607 <--
	US 5879700	A	19990309	US 1995-480456	19950607 <--
	US 5756116	A	19980526	US 1996-758501	19961202 <--
	US 6015573	A	20000118	US 1997-991740	19971216 <--
PRAI	US 1991-777683	B2	19911015	<--	
	US 1993-60258	A2	19930512	<--	
	US 1996-758501	A1	19961202	<--	

OS CASREACT 126:70124

OSC.G 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)

RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 16 OF 21 HCAPLUS COPYRIGHT 2009 ACS on STN

TI Biochemical basis for increased susceptibility to cidofovir of herpes simplex viruses with altered or deficient thymidine kinase activity

AB It has been observed that herpes simplex virus mutants with deficient or altered thymidine kinase activity are more susceptible to cidofovir {CDV; 1-[{S}-3-hydroxy-2-(phosphonomethoxy)propyl]cytosine dihydrate} in tissue culture than are the parental strains. During infection of cells, the elevation of the dCTP pool by thymidine kinase mutant viruses is less than that induced by the wild-type virus. The competition between CDV diphosphate and dCTP at the viral polymerase is therefore changed in favor of CDV diphosphate, enhancing its activity.

AN 1995:788357 HCAPLUS <<LOGINID::20091214>>

DN 123:187816

OREF 123:33073a,33076a

TI Biochemical basis for increased susceptibility to cidofovir of herpes simplex viruses with altered or deficient thymidine kinase activity

AU Mendel, Dirk B.; Bakhimer, David B.; Chen, Ming S.

CS Dep. Biochemistry and Virology, Gilead Sciences, Foster City, CA, 94404, USA

SO Antimicrobial Agents and Chemotherapy (1995), 39(9), 2120-2  
CODEN: AMACQ; ISSN: 0066-4804

PB American Society for Microbiology

DT Journal

LA English

OSC.G 19 THERE ARE 19 CAPLUS RECORDS THAT CITE THIS RECORD (19 CITINGS)

L9 ANSWER 17 OF 21 HCAPLUS COPYRIGHT 2009 ACS on STN  
TI Acyclovir derivatives and other nucleoside analogs for topical treatment of herpes infection

AB Compns. for topical use in herpes virus infections comprise anti-herpes nucleoside analog phosphate esters, e.g. acyclovir monophosphate and acyclovir diphosphate, which show increased activity against native strains of herpes virus as well as against resistant strains, particularly thymidine kinase neg. strains of virus. Also disclosed are methods for using the topical compns. in treatment of herpes disease.

AN 1995:426687 HCAPLUS <<LOGINID::20091214>>

DN 123:102760

OREF 123:18027a,18030a

TI Acyclovir derivatives and other nucleoside analogs for topical treatment of herpes infection

IN Hostetler, Karl Y.

PA USA

SO PCT Int. Appl., 36 pp.  
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9426273	A1	19941124	WO 1993-US4450	19930512 <--
	W: AU, CA, JP				
	RW: AT, BE, CH, CA 2162574	DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE	19941124	CA 1993-2162574	19930512 <--
	AU 9343721	A	19941212	AU 1993-43721	19930512 <--
	AU 701574	B2	19990204		
	JP 08510236	T	19961029	JP 1993-525361	19930512 <--
	EP 746319	A1	19961211	EP 1993-913832	19930512 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
PRAI	WO 1993-US4450	A	19930512 <--		

OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 18 OF 21 HCAPLUS COPYRIGHT 2009 ACS on STN

TI In vivo antiherpesvirus activity of N-7-substituted acyclic nucleoside analog 2-amino-7-[(1,3-dihydroxy-2-propoxy)methyl]purine

AB The efficacy of 2-amino-7-[(1,3-dihydroxy-2-propoxy)methyl]purine (S2242) was evaluated in several animal models for herpesvirus infections. Compound S2242 was more effective than acyclovir (i) when administered s.c. in a model for herpes simplex virus type 1 (HSV-1)-induced mortality in immunocompetent mice and (ii) when applied topically to hairless (hr/h) mice that had been infected intracutaneously with HSV-2. In SCID (Severe combined immune deficient) mice that had been infected with a thymidine kinase-deficient HSV-1 strain, S2242 (administered s.c. at a dosage of 50 mg/kg/day) completely protected against virus-induced mortality whereas foscarnet was less effective and acyclovir had no or little protective effect. Compound S2242 was far more effective than ganciclovir in preventing or delaying murine cytomegalovirus-induced mortality in immunocompetent and SCID mice. The compound was more effective when a given dose was fractionated and administered on subsequent days than when this dose was administered in one single injection. A 5-day treatment course with S2242 (10 and 50 mg/kg/day) for newborn mice that had been infected with a LD of murine cytomegalovirus suppressed virus-induced mortality. Compound S2242 had no

inhibitory effect on the growth of weanling (at 50 mg/kg for 5 days) and 3- to 4-wk-old mice (at doses of 50 to 200 mg/kg for 6 wk). However, akin to ganciclovir, compound S2242 significantly reduced testicle weight, testicle morphol., and spermatogenesis.

AN 1995:276710 HCAPLUS <>LOGINID::20091214>>  
DN 122:95914  
OREF 122:17879a,17882a  
TI In vivo antiherpesvirus activity of N-7-substituted acyclic nucleoside analog 2-amino-7-[(1,3-dihydroxy-2-propoxy)methyl]purine  
AU Neyts, Johan; Jaehne, Gerhard; Andrei, Graciela; Snoeck, Robert; Winkler, Irvin; De Clercq, Erik  
CS Rega Inst. Med. Res., Katholieke Univ. Leuven, Louvain, B-3000, Belg.  
SO Antimicrobial Agents and Chemotherapy (1995), 39(1), 56-60  
CODEN: AMACQ; ISSN: 0066-4804  
PB American Society for Microbiology  
DT Journal  
LA English

OSC.G 17 THERE ARE 17 CAPLUS RECORDS THAT CITE THIS RECORD (17 CITINGS)

L9 ANSWER 19 OF 21 HCAPLUS COPYRIGHT 2009 ACS on STN  
TI Inhibitors of bovine herpes mammillitis virus infections in cultured cells and in vaginally infected guinea pigs  
AB Bovine herpes mammillitis virus or bovine herpesvirus type 2 (BHV-2) causes ulcerative lesions on the teats and udders of infected cows. The authors investigated several nucleoside and nucleotide analogs as potential BHV-2 inhibitors. These included acyclovir, ganciclovir, 5-ido-2'-deoxyuridine (IUdR), 1-(2'-deoxy-2'-fluoro- $\beta$ -D-arabinofuranosyl) derivs. of 5-iodocytosine (FIAC), 5-iodouracil (FIAU), and 5-methyluracil (FMAU), and various 3-hydroxyphosphonylmethoxypropyl (HPMP) and 2-phosphonylmethoxyethyl (PME) derivs. of adenine (A), guanine (G), 2,6-diaminopurine (DAP), and/or cytosine (C). Of these, FIAU and FMAU were the most potent in cell culture, inhibiting 50% of BHV-2 plaques at <0.05  $\mu$ M. HPMPA and HPMPG were active at 0.3  $\mu$ M; FIAC, IUdR, and HPMPC at 1.3-2.3  $\mu$ M; PMEDAP and ganciclovir at 20-25  $\mu$ M; acyclovir and PMEA at >100  $\mu$ M. The two most potent agents, FIAU and FMAU, inhibited uninfected embryonic bovine tracheal cell growth by 50% at >100  $\mu$ M and 53  $\mu$ M, resp., resulting in selectivity indexes (ratio of the 50% inhibitory concentration for cell growth to the 50% inhibitory concentration for plaque formation) of >2200 and 1100. Greater degrees of antiviral activity and selectivity were obtained in infected guinea pig embryo cells treated with FIAU, FMAU, and HPMPC. Infected cell exts. containing BHV-2-induced thymidine kinase activity phosphorylated FIAU, FMAU, and IUdR at nearly the same rate as thymidine, whereas FIAC, acyclovir, and ganciclovir were phosphorylated at  $\leq$ 5% the rate of thymidine. Phosphorylation by this enzyme is required to generate the antivirally active nucleoside triphosphate in infected cells. In guinea pigs infected intravaginally with BHV-2, FMAU treatments of 1, 3.2, and 10 mg kg<sup>-1</sup> per day for 5 days starting 1 day after virus challenge reduced vaginal lesion scores and virus titers in a dose-dependent manner. FIAU (10  $\mu$ M) was as effective as 1  $\mu$ M FMAU by the same regimen. A single treatment with 10  $\mu$ M HPMPC was as active as daily treatments with 3.2 mg FMAU kg<sup>-1</sup>. These results indicate the potential of using antiviral agents to treat bovine herpes mammillitis virus infections in cattle, and the application of guinea pigs to study BHV-2 disease.

AN 1994:671329 HCAPLUS <>LOGINID::20091214>>  
DN 121:271329  
OREF 121:49243a,49246a  
TI Inhibitors of bovine herpes mammillitis virus infections in cultured cells and in vaginally infected guinea pigs  
AU Smee, D. F.; Leonhardt, J. A.; Sugiyama, S. T.; Holy, A.

CS Inst. Antiviral Res., Utah State Univ., Logan, UT, 84322-5600, USA  
SO Antiviral Chemistry & Chemotherapy (1994), 5(4), 201-8  
CODEN: ACCHEH; ISSN: 0956-3202  
DT Journal  
LA English

L9 ANSWER 20 OF 21 HCPLUS COPYRIGHT 2009 ACS on STN  
TI Antiviral activities of guanosine analogs in guinea pig embryonic fibroblasts  
AB Previous research has shown that certain antiherpes substances that are activated by thymidine kinase are substantially more active in human fibroblasts than in green monkey kidney cells. The difference has been attributed to the presence of large amounts of intracellular thymidine in the latter cell type. Antiviral guanosine analogs but not thymidine analogs show decreased antiviral activity when used in herpes simplex virus type 1-infected guinea pig fibroblasts. The intracellular pools of antiviral di- and triphosphate nucleotides, the monophosphate nucleotide phosphorylating enzyme activities, and the antiviral triphosphate nucleotide stability, studied in herpes simplex virus type 1-infected and uninfected guinea pig fibroblasts are reported. The results were compared with results of parallel experiments done with human fibroblasts and green monkey kidney cells.  
AN 1989:303 HCPLUS <>LOGINID::20091214>>  
DN 110:303  
OREF 110:43a, 46a  
TI Antiviral activities of guanosine analogs in guinea pig embryonic fibroblasts  
AU Harmenberg, Johan; Stenberg, Kjell  
CS Dep. Virol., Natl. Bacteriol. Lab., Stockholm, S-105 21, Swed.  
SO Antimicrobial Agents and Chemotherapy (1988), 32(10), 1533-6  
CODEN: AMACQ; ISSN: 0066-4804  
DT Journal  
LA English

L9 ANSWER 21 OF 21 HCPLUS COPYRIGHT 2009 ACS on STN  
TI Potent activity of 5-fluoro-2'-deoxyuridine and related compounds against thymidine kinase-deficient (TK-) herpes simplex virus: targeted at thymidylate synthase  
AB 5-Fluorouracil, 5-fluorouridine (FUrd), 5-fluoro-2'-deoxyuridine (FdUrd), 5-fluorocytidine (FCyd), 5-fluoro-2'-deoxycytidine (FdCyd), 5-trifluoro-2'-deoxythymidine (F3dTdh), and the 5'-monophosphates and 3',5'-cyclic monophosphates of these compounds. inhibited thymidine kinase-deficient (TK-) mutant strains of herpes simplex virus (HSV) at a much lower concentration than the wild-type (TK+) HSV strains. Other 5-substituted 2'-deoxyuridines which have been previously recognized as potent thymidylate synthase inhibitors behaved in a similar fashion. The activity of FdUrd, FdCyd, F3dTdh, and their 3',5'-cyclic monophosphates against TK-HSV was readily reversed by 2'-deoxytymidylate (dTdh) but not by 2'-deoxyuridine (dUrd). These compounds also inhibited the incorporation of [6-3H]dUrd into DNA at a concentration which was up to 5 orders of magnitude lower than the concentration at which the incorporation of [methyl-3H] dThd was inhibited. Thus, while not being a target for the well established anti-HSV compounds. in TK+HSV-infected cells, thymidylate synthase appears to be an important target in TK-HSV-infected cells. In addition to dTMP synthase, TK-HSV-infected cells appear to reveal other therapeutically exploitable targets such as OMP decarboxylase (towards pyrazofurin), CTP synthase (towards carbodine and its cyclopentenyl analog), dihydrofolate reductase (towards methotrexate), and S-adenosylhomocysteine hydrolase (towards neplanocins).  
AN 1988:142897 HCPLUS <>LOGINID::20091214>>  
DN 108:142897

OREF 108:23267a,23270a  
TI Potent activity of 5-fluoro-2'-deoxyuridine and related compounds against thymidine kinase-deficient (TK-) herpes simplex virus: targeted at thymidylate synthase  
AU De Clercq, Erik; Beres, Jozsef; Bentruude, Wesley G.  
CS Rega Inst. Med. Res., Katholieke Univ. Leuven, Leuven, B-3000, Belg.  
SO Molecular Pharmacology (1987), 32(2), 286-92  
CODEN: MOPMA3; ISSN: 0026-895X  
DT Journal  
LA English  
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

=> d his

(FILE 'HOME' ENTERED AT 09:57:53 ON 14 DEC 2009)

FILE 'HCAPLUS' ENTERED AT 09:57:59 ON 14 DEC 2009

FILE 'REGISTRY' ENTERED AT 09:58:12 ON 14 DEC 2009  
EXP ACYCLOVIR MONOPHOSPHATE/CN

L1 1 S E3  
EXP GANCYCLOVIR MONOPHOSPHATE/CN  
EXP GANCICLOVIR MONOPHOSPHATE/CN  
EXP GANCICLOVIR- MONOPHOSPHATE/CN  
EXP GANCICLOVIR-O-MONOPHOSPHATE/CN  
EXP GANCICLOVIR/CN  
EXP CIDOFOOVIR/CN

L2 1 S E4  
EXP FOSCARNET/CN

L3 1 S E3

FILE 'HCAPLUS' ENTERED AT 10:00:25 ON 14 DEC 2009

L4 1216 S L1/THU OR L2/THU OR L3/THU  
L5 30155 S HERPES  
L6 218 S L4 AND L5  
L7 128 S L6 AND (PY<2003 OR AY<2003 OR PRY<2003)  
L8 10740 S THYMIDINE KINASE  
L9 21 S L7 AND L8

=> log hold

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	68.70	89.74
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-17.22	-17.22

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STN INTERNATIONAL SESSION SUSPENDED AT 10:01:32 ON 14 DEC 2009

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PASSWORD:

\* \* \* \* \* RECONNECTED TO STN INTERNATIONAL \* \* \* \* \*  
SESSION RESUMED IN FILE 'HCAPLUS' AT 10:15:35 ON 14 DEC 2009  
FILE 'HCAPLUS' ENTERED AT 10:15:35 ON 14 DEC 2009  
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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	68.70	89.74
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-17.22	-17.22

=> s (gancyclovir or ganciclovir) (2a) (phosphate or monophosphate)  
400 GANCYCLOVIR  
4274 GANCICLOVIR  
643735 PHOSPHATE  
35385 MONOPHOSPHATE  
L10 27 (GANCYCLOVIR OR GANCICLOVIR) (2A) (PHOSPHATE OR MONOPHOSPHATE)

=> s herpes or herpesvirus  
30155 HERPES  
34376 HERPESVIRUS  
L11 51214 HERPES OR HERPESVIRUS

=> s l10 and l11  
L12 10 L10 AND L11

=> s l12 and (PY<2003 or AY<2003 or PRY<2003)  
23001885 PY<2003  
4531634 AY<2003  
4001927 PRY<2003  
L13 9 L12 AND (PY<2003 OR AY<2003 OR PRY<2003)

=> d l13 1-9 ti abs bib

L13 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN  
TI Role of the human herpesvirus 6 U69-encoded kinase in the phosphorylation of ganciclovir  
AB The human herpesvirus 6 (HHV-6) U69 gene product (pU69) is the presumed functional homolog of the human cytomegalovirus (HCMV) UL97-encoded kinase (pUL97), which converts ganciclovir to its monophosphate metabolite in HCMV-infected cells. It has been reported that insertion of U69 into baculovirus confers sensitivity to ganciclovir in insect cells (J Virol 73:3284-3291, 1999). Our metabolic studies in HHV-6-infected human T-lymphoblast cells indicated that the efficiency of ganciclovir phosphorylation induced by HHV-6 was relatively poor. Recombinant vaccinia viruses (rVV), expressing high levels of pU69 from two HHV-6 strains (representing the A and B variant), were constructed and used to compare the ganciclovir-phosphorylating capacity of pU69 and pUL97 in human cells. Metabolic studies with [<sup>3</sup>H]ganciclovir showed that ganciclovir was phosphorylated in human cells infected with pU69-expressing rVV, although the levels of phosphorylated ganciclovir metabolites were approx. 10-fold lower than those observed with pUL97. We also demonstrated that pU69, like pUL97, is expressed as a nuclear protein. Our results indicate that the limited phosphorylation of ganciclovir by pU69 may contribute to its modest antiviral activity against HHV-6 in certain cell systems.  
AN 2002:646596 HCAPLUS <<LOGINID::20091214>>

DN 138:231310  
TI Role of the human herpesvirus 6 U69-encoded kinase in the phosphorylation of ganciclovir  
AU De Bolle, Leen; Michel, Detlef; Mertens, Thomas; Manichanh, Chaysavanh; Agut, Henri; De Clercq, Erik; Naesens, Lieve  
CS Rega Institute for Medical Research, Katholieke Universiteit Leuven, Louvain, Belg.  
SO Molecular Pharmacology (2002), 62(3), 714-721  
CODEN: MOPMA3; ISSN: 0026-895X  
PB American Society for Pharmacology and Experimental Therapeutics  
DT Journal  
LA English  
OSC.G 18 THERE ARE 18 CAPLUS RECORDS THAT CITE THIS RECORD (18 CITINGS)  
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN  
TI Viral and host-cell protein kinases: enticing antiviral targets and relevance of nucleoside, and viral thymidine kinases  
AB A review with many refs. Numerous targets are known for development of antiviral agents, and some significant successes have been achieved with nucleoside analogs. These are "activated" by phosphorylation by viral and/or host-cell nucleoside kinases, the final target being principally the viral polymerase. With latency of herpes viruses, the viral thymidine kinase may be the ultimate target. Less attention has been devoted to viral protein kinases as antiviral targets, largely because 5 yr ago, these the study of such enzymes was considered "still in its infancy.". In the interim, identification of viral and host-cell protein kinases involved in viral gene expression, and viral replication, has made impressive advances. In conjunction with current progress in development of specific inhibitors of cellular protein kinases, and the differences in sequence motifs between these and the viral enzymes, the latter are indeed attractive targets, as are also some host-cell protein kinases. Examples include, amongst others, the essential protein kinases of vaccinia virus; the nonsegmented neg.-strand RNA viruses, all essentially dependent on host-cell kinases, e.g., protein kinase CK-II (casein kinase-II), for which good inhibitors, such as halogenated benzimidazoles and benzotriazoles, are known; herpes viruses, with emphasis on human cytomegalovirus, the UL97 gene of which codes for a protein kinase that, like viral thymidine kinases, "activates," by phosphorylation, a nonpeptide antiviral acyclonucleoside ganciclovir, an analog of the antiherpes acyclovir. The latter, in turn, is active against animal cytomegaloviruses following phosphorylation by the products of their UL97 gene homologues. Attention is also directed to the antiviral activity of the cyclic phosphate of ganciclovir, a structural analog of the second messenger cyclic GMP.  
AN 1999:397270 HCAPLUS <<LOGINID::20091214>>  
DN 131:179170  
TI Viral and host-cell protein kinases: enticing antiviral targets and relevance of nucleoside, and viral thymidine kinases  
AU Shugar, David  
CS Institute of Biochemistry and Biophysics, Polish Academy of Sciences (PAS), Warsaw, 02-106, Pol.  
SO Pharmacology & Therapeutics (1999), 82(2-3), 315-335  
CODEN: PHTHDT; ISSN: 0163-7258  
PB Elsevier Science Inc.  
DT Journal; General Review  
LA English  
OSC.G 28 THERE ARE 28 CAPLUS RECORDS THAT CITE THIS RECORD (28 CITINGS)  
RE.CNT 130 THERE ARE 130 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN  
 TI Nucleoside analog phosphates for topical use in the treatment of herpes virus infections  
 AB Compns. for topical use in herpes virus infections comprise anti-herpes nucleoside analog phosphate esters, e.g. acyclovir monophosphate, acyclovir diphosphate, and acyclovir triphosphate which show increased activity against native strains of herpes virus as well as against resistant strains, particularly thymidine kinase neg. strains of virus. Also disclosed are methods for treatment of herpes infections with nucleoside phosphates. Anti-herpes nucleoside analogs phosphate esters include the phosphoramidates and phosphothiorates, as well as polyphosphates comprising C and S bridging atoms.  
 AN 1999:175589 HCAPLUS <<LOGINID::20091214>>  
 DN 130:218263  
 TI Nucleoside analog phosphates for topical use in the treatment of herpes virus infections  
 IN Hostetler, Karl Y.  
 PA USA  
 SO U.S., 19 pp., Cont.-in-part of U.S. 5,580,571.  
 CODEN: USXXAM  
 DT Patent  
 LA English  
 FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5879700	A	19990309	US 1995-480456	19950607 <--
	US 5580571	A	19961203	US 1993-60258	19930512 <--
	CA 2222154	A1	19961219	CA 1996-2222154	19960606 <--
	WO 9640088	A1	19961219	WO 1996-US10085	19960606 <--
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
	AU 9663842	A	19961230	AU 1996-63842	19960606 <--
	EP 831794	A1	19980401	EP 1996-923289	19960606 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	CN 1192138	A	19980902	CN 1996-195922	19960606 <--
	JP 11507642	T	19990706	JP 1997-502194	19960606 <--
	CN 1221609	A	19990707	CN 1998-123863	19981030 <--
PRAI	US 1991-777683	B2	19911015	<--	
	US 1993-60258	A2	19930512	<--	
	US 1995-480456	A	19950607	<--	
	WO 1996-US10085	W	19960606	<--	

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN  
 TI Oxyalkylene phosphate compounds and therapeutic uses thereof  
 AB Compns. and methods are provided for treating, preventing or ameliorating cancer and other proliferative diseases, as are methods of inducing wound healing, treating cutaneous ulcers, treating gastrointestinal disorders, treating blood disorders such as anemias, immunomodulation, enhancing recombinant gene expression, treating insulin-dependent patients, treating cystic fibrosis patients, inhibiting telomerase activity, treating virus-associated tumors, especially EBV-associated tumors, modulating gene expression

and in particular, augmenting expression of tumor suppressor genes, inducing tolerance to antigens, treating, preventing or ameliorating protozoan infection, or inhibiting histone deacetylase in cells. The compns. of the invention are to and the methods of the invention use oxyalkalene phosphate compds.

AN 1998:621122 HCAPLUS <<LOGINID::20091214>>  
DN 129:239917  
OREF 129:48679a, 48682a  
TI Oxyalkylene phosphate compounds and therapeutic uses thereof  
IN Nudelman, Abraham; Rephaeli, Ada  
PA Beacon Laboratories, L.L.C., USA  
SO PCT Int. Appl., 92 pp.  
CODEN: PIXXD2

DT Patent  
LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9840080	A1	19980917	WO 1998-US4834	19980311 <--
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 6030961	A	20000229	US 1997-814386	19970311 <--
	CA 2283162	A1	19980917	CA 1998-2283162	19980311 <--
	AU 9864597	A	19980929	AU 1998-64597	19980311 <--
	EP 986391	A1	20000322	EP 1998-910333	19980311 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2001514665	T	20010911	JP 1998-539793	19980311 <--
	IL 131742	A	20051120	IL 1998-131742	19980311 <--
PRAI	US 1997-814386	A	19970311 <--		
	WO 1998-US4834	W	19980311 <--		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OS MARPAT 129:239917

OSC.G 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN  
TI Superior cytotoxicity with ganciclovir compared with acyclovir and 1- $\beta$ -D-arabinofuranosylthymine in herpes simplex virus-thymidine kinase-expressing cells: a novel paradigm for cell killing  
AB Enzyme-prodrug therapy using ganciclovir and herpes simplex virus-thymidine kinase (HSV-TK) has demonstrated excellent antitumor activity in many different types of malignant cells. Previously, the authors noted that ganciclovir was substantially more cytotoxic than other HSV-TK substrates. Therefore, the authors embarked on a study to determine the basis for the superior cytotoxicity of ganciclovir. In U251tk human glioblastoma cells that stably express HSV-TK, ganciclovir elicited a >4 log cell kill instead of the  $\leq$ 1.5 log cell kill mediated by two other HSV-TK substrates, 1- $\beta$ -D-arabinofuranosylthymine (araT) and acyclovir. Study of the metabolism of these drugs demonstrated that acyclovir was poorly phosphorylated to its active triphosphate with DNA incorporation below the limit of detection, which may explain the <1 log cell kill in these cells. Lower levels of ganciclovir triphosphate accumulated compared with araT triphosphate (araTPP) under conditions that

induced  $\geq 1$  log cell kill (67 vs. 1235 pmol/107 cells, resp.), and the half-life for the triphosphate of ganciclovir was shorter than that of araT (terminal half-lives of 15 and 41 h, resp.). Incorporation of ganciclovir monophosphate into DNA was less than that of araT monophosphate, and both analogs were retained in DNA for  $\geq 48$  h. Thus, the superior cytotoxicity of ganciclovir was not due to enhanced metabolism to active forms. Highly cytotoxic concns. of ganciclovir produced only weak inhibition of DNA synthesis. This allowed cells to proceed through S and G2-M phases during and after drug exposure, resulting in a doubling of cell number by 48 h after drug washout. As they attempted to progress through the cell cycle a second time, ganciclovir-treated cells accumulated in early S-phase and remained there until cell death, suggesting that ganciclovir incorporation in the DNA template was important for cytotoxicity. In contrast, strong inhibition of DNA synthesis by araTPP prevented cells from traversing the cell cycle for at least 12 h after drug washout, when the active metabolite was largely degraded. AraT-treated cells were unable to divide for at least 72 h after drug exposure, at which point the surviving cells displayed a normal cell cycle distribution pattern. Based on the results presented here, the authors propose a novel paradigm in which the ability of ganciclovir to incorporate into DNA without inhibiting progression through S-phase, combined with high cytotoxicity for incorporated ganciclovir monophosphate, produces multilog cytotoxicity.

AN 1998:588895 HCPLUS <>LOGINID::20091214>>  
DN 129:298069  
OREF 129:60648h, 60649a  
TI Superior cytotoxicity with ganciclovir compared with acyclovir and 1- $\beta$ -D-arabinofuranosylthymine in herpes simplex virus-thymidine kinase-expressing cells: a novel paradigm for cell killing  
AU Rubsam, Laura Z.; Davidson, Beverly L.; Shewach, Donna S.  
CS Department of Pharmacology, University of Michigan Medical Center, Ann Arbor, MI, 48109-0504, USA  
SO Cancer Research (1998), 58(17), 3873-3882  
CODEN: CNREA8; ISSN: 0008-5472  
PB American Association for Cancer Research  
DT Journal  
LA English  
OSC.G 53 THERE ARE 53 CAPLUS RECORDS THAT CITE THIS RECORD (53 CITINGS)  
RE.CNT 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT  
  
L13 ANSWER 6 OF 9 HCPLUS COPYRIGHT 2009 ACS on STN  
TI Differential ganciclovir-mediated cytotoxicity and bystander killing in human colon carcinoma cell lines expressing herpes simplex virus thymidine kinase  
AB The two human colon carcinoma cell lines HT-29 and SW620, which stably express herpes simplex virus thymidine kinase (HSV-TK), are sensitized to the cytotoxic effects of the antiviral drug ganciclovir (GCV). Compared with HT-29 cells, SW620 cells were more sensitive to lower GCV concns. ( $<1 \mu\text{M}$ ), accumulated GCV triphosphate more rapidly, and incorporated higher levels of GCV into DNA. Following a 24-h exposure to 10  $\mu\text{M}$  GCV, bystander killing was as much as sixfold greater in SW620 cells than HT-29 cells. This bystander effect was dependent on the level of HSV-TK expression, the number of cells expressing HSV-TK, and the overall confluence of the cells. However, bystander killing did not correlate with gap junctional intercellular communication as determined by microinjection of Lucifer Yellow fluorescent dye. SW620 cells were coupled to  $<3\%$  adjacent cells (compared with  $>50\%$  for HT-29 cells), but were still able to transfer phosphorylated GCV to bystander cells as soon as 4 h after drug was added. These results emphasize the importance of cell-specific metabolism in HSV-TK/GCV-mediated cytotoxicity and may suggest a novel

mechanism for bystander killing.

AN 1998:258436 HCPLUS <<LOGINID::20091214>>

DN 129:22960

OREF 129:4739a, 4742a

TI Differential ganciclovir-mediated cytotoxicity and bystander killing in human colon carcinoma cell lines expressing herpes simplex virus thymidine kinase

AU Boucher, Paul D.; Ruch, Randall J.; Shewach, Donna S.

CS Department of Pharmacology, University of Michigan Medical Center, Ann Arbor, MI, 48109, USA

SO Human Gene Therapy (1998), 9(6), 801-814

CODEN: HGTHE3; ISSN: 1043-0342

PB Mary Ann Liebert, Inc.

DT Journal

LA English

OSC.G 47 THERE ARE 47 CAPLUS RECORDS THAT CITE THIS RECORD (47 CITINGS)

RE.CNT 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 7 OF 9 HCPLUS COPYRIGHT 2009 ACS on STN

TI Synthesis and antiviral activity of alkoxypropyl esters of ganciclovir monophosphate in HCMV- and HSV-infected cells

AB Ganciclovir has proven to be an effective treatment for cytomegalovirus disease in humans (HCMV). However, the oral bioavailability of ganciclovir is only 6 to 9 percent and the plasma half-life is short, 2.9 h. In an attempt to develop a prodrug of this agent with improved pharmacokinetics, we synthesized 1, a ganciclovir monophosphate-lipid conjugate, and tested it for inhibitory activity against HCMV and herpes simplex virus (HSV-1) in DNA-reduction assays. Conjugate 1 is 6-fold more potent than ganciclovir in the HCMV assay ( $IC_{50} = 0.3 \mu M$ ). Ganciclovir and 1 are equally active against HSV-1. The synthesis and evaluation of 1 will be presented.

AN 1997:162100 HCPLUS <<LOGINID::20091214>>

TI Synthesis and antiviral activity of alkoxypropyl esters of ganciclovir monophosphate in HCMV- and HSV-infected cells

AU Beadle, James R.; Kini, Ganesh D.; Aldern, Kathy A.; Hostetler, Karl Y.

CS Department Medicine, VA Medical Center, San Diego, CA, 92161, USA

SO Book of Abstracts, 213th ACS National Meeting, San Francisco, April 13-17 (1997), MEDI-268 Publisher: American Chemical Society, Washington, D. C.

CODEN: 64AOAA

DT Conference; Meeting Abstract

LA English

L13 ANSWER 8 OF 9 HCPLUS COPYRIGHT 2009 ACS on STN

TI Ganciclovir-induced ablation of non-proliferating thyrocytes expressing herpesvirus thymidine kinase occurs by p53-independent apoptosis

AB In adult mice of the transgenic strain TG66.19, in which expression of herpes simplex type 1 virus thymidine kinase (HSV1-TK) is driven in thyrocytes from the thyroglobulin promoter, the drug Ganciclovir causes the death (ablation) of thyrocytes. Ablation occurred in the absence of thyrocyte proliferation or nuclear DNA synthesis, but was accompanied by transient expression of proliferating cell nuclear antigen and the dying thyrocytes exhibited the ultrastructural features of apoptosis. Control expts. show that the apoptosis is a result of the production of Ganciclovir phosphates in thyrocytes that express HSV1-TK. However, cell death was not dependent upon the presence of a functional copy of the oncosuppressor gene p53. We conclude that the apoptosis is probably not mediated by induction of DNA damage and occurs via a pathway that is independent of

p53. The fact that Ganciclovir phosphate can kill cells by a p53-independent apoptotic pathway is encouraging in relation to tumor ablation by methods based on transfection with HSV1-tk and administration of Ganciclovir.

AN 1996:463408 HCAPLUS <<LOGINID::20091214>>  
DN 125:157902  
OREF 125:29255a,29258a  
TI Ganciclovir-induced ablation of non-proliferating thyrocytes expressing herpesvirus thymidine kinase occurs by p53-independent apoptosis  
AU Wallace, Helen; Clarke, Alan R.; Harrison, David J.; Hooper, Martin L.; Bishop, John O.  
CS Cent. Genome Res., Univ. Edinburgh, Edinburgh, EH9 3JQ, UK  
SO Oncogene (1996), 13(1), 55-61  
CODEN: ONCNES; ISSN: 0950-9232  
PB Stockton  
DT Journal  
LA English

OSC.G 37 THERE ARE 37 CAPLUS RECORDS THAT CITE THIS RECORD (37 CITINGS)

L13 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN  
TI Herpes simplex virus type 1 and human DNA polymerase interactions with 2'-deoxyguanosine 5'-triphosphate analogs. Kinetics of incorporation into DNA and induction of inhibition  
AB The ability of herpes simplex virus type 1 (HSV-1) DNA polymerase, HeLa polymerase  $\alpha$ , and HeLa polymerase  $\beta$  to utilize several dGTP analogs was investigated using a defined synthetic template primer. The relative efficiencies of the triphosphates of 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir triphosphate, ACVTP), 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (ganciclovir triphosphate, DPGTTP), and 2',3'-dideoxyguanosine (ddGTP) as substrates for the 3 polymerases were: HSV-1 polymerase, dGTP > ACVTP = DPGTTP > ddGTP; polymerase  $\alpha$ , dGTP > ACVTP = DPGTTP » ddGTP; polymerase  $\beta$ , ddGTP > dGTP » ACVTP = DPGTTP. The potent inhibition of HSV-1 polymerase by ACVTP is due to the formation of a dead-end complex upon binding of the next 2'-deoxynucleoside 5'-triphosphate encoded by the template after incorporation of acyclovir monophosphate into the 3' end of the primer. This mechanism was shown here to be a general mechanism for inhibition of polymerases by the obligate chain terminators, ACVTP and deGTP. The ACVTP-induced inhibition was 30-fold more potent with HSV-1 polymerase than with polymerase  $\alpha$ . This difference may contribute to the antiviral selectivity of this nucleotide analog. The effect of ganciclovir monophosphate incorporation (a nonobligate chain terminator) on subsequent primer extension was also evaluated. With HSV-1 polymerase and polymerase  $\alpha$ , although there was a considerable reduction in the efficiency of utilization of the 3'-DGTGMP-terminal primer, contrasting kinetic behavior was subsequent nucleotide incorporations. In contrast, with polymerase  $\alpha$ , a relatively small decrease in Vmax was accompanied by increased Km values for subsequent nucleotide incorporations.

AN 1989:586925 HCAPLUS <<LOGINID::20091214>>  
DN 111:186925  
OREF 111:30863a,30866a  
TI Herpes simplex virus type 1 and human DNA polymerase interactions with 2'-deoxyguanosine 5'-triphosphate analogs. Kinetics of incorporation into DNA and induction of inhibition  
AU Reardon, John E.  
CS Exp. Ther. Div., Wellcome Res. Lab., Research Triangle Park, NC, 27709, USA  
SO Journal of Biological Chemistry (1989), 264(32), 19039-44  
CODEN: JBCHA3; ISSN: 0021-9258  
DT Journal

LA English  
OSC.G 58 THERE ARE 58 CAPLUS RECORDS THAT CITE THIS RECORD (58 CITINGS)